AUDITORY PROCESSING IN THE SYNDROME OF INFANTILE SPASMS

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ABSTRACT

The early onset epileptic encephalopathy of infantile spasms is frequently associated with acute cognitive regression, long-term learning disability and autistic spectrum disorder. Although there may be a structural basis to the epilepsy, it appears that seizure activity is directly implicated in the process associated with the above disabilities. There are strong indications of the crucial role of temporal lobe dysfunction in children within this and related epileptic regressions; including the site of lesions in tuberous sclerosis and the EEG localisation in a later onset epileptic encephalopathy, the Landau-Kleffner-syndrome. Thus the hypothesis for this study was that the temporal lobe is functionally abnormal in children with infantile spasms. This was tested by recording event related potentials, the electrical indicators of the brain's perception and processing of auditory stimuli. The aims of the current study were to describe the normal developmental changes of mismatch-negativity (MMN) and novelty P3 in the first year of life and to identify whether these ERPs are abnormal in children with infantile spasms. The developmental status of infants with infantile spasms was assessed at presentation.

The MMN was only shown in a group mean average in control infants. All obligatory and the endogenous P250, P500, Nc1 and Nc2 ERP components of the control infants showed age dependent latencies and differed in latency between wakefulness and stage 2 sleep. Using nonparametric calculations infants with infantile spasms had prolonged latencies of the obligatory and endogenous components during both wakefulness and sleep compared to controls.

The results of this study support the hypothesis that the auditory processing is interrupted in infants with infantile spasms. As the auditory cortex is very immature during the first year of life it is therefore suggested that infantile spasms may interfere with crucial maturational processes during the first year of life.

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PERSONAL CONTRIBUTIONS OF THE CANDIDATE

Chapter 1	Literature review
Chapter 2	Literature review
Chapter 3	Recruiting of all control infants
	Recording of all control infants and infants with infantile spasms
	Gross developmental screening in infants with infantile spasms
	Analysis of ERP components in control infants and infants with infantile spasms
	Calculation of signal to noise ratio
	Statistical analysis of control infants, received support in analysing statistically the ERP data and SNR of infants with infantile spasms when using logistic regression
Chapter 4	Discussion of ERP results in control population
Chapter 5	Discussion of ERP results in patients with infantile spasms

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CONTENTS

INDEX OF FIGURES

INDEX OF TABLES

CHAPTER 1: INTRODUCTION

1.1. Epileptic encephalopathies

1.1.1. *Definition of epilepsy and epileptic encephalopathy*

Epilepsy is defined as a chronic condition, characterized by recurrent epileptic seizures, which are clinical events associated with hypersynchronous, usually self-limited, activity of neurons in the brain (Blume *et al.,* 2001). Epilepsy is the most common potentially treatable serious neurological disorder in children and young adults affecting 1-2 % of the total population (Hauser, 1990) and 4% of children (Hauser, 1995). The incidence of epilepsy is greatest in the first year of life, remains high up to 4 years of age, falls during childhood and declines more slowly during adolescence and adult life with a second peak in older people.

Children with epilepsy have more behavioural and cognitive problems than children with other non neurological chronic illnesses and children in the general population (Dunn *et al.,* 1999). They are also more likely to suffer from a psychiatric disorder than children in the general population or even those with other types of chronic illness (Davies *et al.,* 2003). Further problems faced by children with epilepsy include educational underachievement and unemployment in adulthood (Aldenkamp *et al.,* 1990; Sillanpaa, 1990; Sillanpaa, 2004).

A severe global cognitive deterioration can occur in infants and young children, in whom frequent seizure activity and subclinical interictal activity may cause a general nervous system dysfunction: a condition referred to as an "epileptic encephalopathy" (EE). The international league against epilepsy (ILAE) has defined epileptic encephalopathy as a condition in which epileptic abnormalities are believed to contribute to the progressive disturbance in cerebral function (Engel, 2001). Several epileptic syndromes, defined as

discreet epilepsy conditions with a complex of clinical and neurophysiological features (Blume *et al.,* 2001), including, Ohtahara syndome, West syndrome, Dravet syndrome or severe myoclonic epilepsy of infancy, Lennox-Gastaut syndrome, the Landau- Kleffner syndrome and epilepsy with continuous spike–waves during slow wave sleep (CSWS) are included in this definition. Early EEs have 4 common features: they begin during infancy or childhood, there is high rate of epileptic discharges, they are often refractory to antiepileptic drugs (AEDs) and there is frequently a poor developmental outcome. All domains of functioning including cognitive, behavioural and motor domains may be affected. Whilst early epileptic encephalopathies have severe cognitive impairment in common, each has its own characteristic clinical features (Wirrell *et al.,* 2005). This study investigated the pathogenesis of these impairments in the most common early onset epilepsy syndrome of infantile spasms.

1.1.1.1. Experimental evidence in animals for seizure induced cognitive impairment

Experimental evidence from animal models has shown that the developing immature brain differs from the adult brain in its susceptibility to seizures, seizure characteristics and responses to AEDs (Holmes, 1997). Compared to the adult brain the immature brain appears to be relatively resistant to seizure induced neuronal injury (Sperber, 1996; Holmes, 1997). Although there is less histological evidence of damaged neurons in the immature brain, there is increasing evidence that seizures may alter the function of surviving neurons and neuronal circuitry to reduce seizure thresholds permanently or promote epileptogenesis (Jensen *et al.,* 1992; Anderson *et al.,* 1997; Jensen *et al.,* 1998; Anderson *et al.,* 1999; Chen *et al.,* 1999). Animals subjected to repeated seizures in early life show significant impairments in learning and memory in adulthood (Huang *et al.,* 1999). The cellular and molecular changes associated with these functional changes are still under investigation. However the experimental findings to date reinforce the concept that seizures can induce long-lasting functional changes in the brain (Huang *et al.,* 1999), which may not appear acutely as injury (Holmes, 1997).

1.1.1.2. Early onset EEs

Early onset EEs are associated with a high rate of cognitive and social impairments. Three retrospective hospital-based studies of outcome from all epilepsies starting in the first year of life have shown mortality to be higher and severe learning disability to be more common in patients with infantile spasms (IS) than in those with febrile seizures, generalised or partial seizures or status epilepticus (Chevrie *et al.,* 1978; Cavazzuti *et al.,* 1984; Dalla *et al.,* 1982). In all three series, factors associated with poor prognosis included a symptomatic cause for the epilepsy and early onset (before the age of 6 months). In a population based retrospective study looking at outcome of seizures occurring in the first years of life, 53% of 40 infants had developmental delay and 50% had abnormal neurological examinations at follow-up. Seizure onset less than 3 months of age, infantile spasms, abnormal neurological examination and epileptic discharges in the EEG at presentation, poor seizure-control and use of more than one AEDS were predictors of uncontrolled epilepsy at follow-up (Datta *et al.,* 2000).

1.1.1.3. Models of epileptic encephalopathy

In epileptic encephalopathies the outcome may not necessarily be related to the severity of the clinical seizures, but to the ongoing subclinical epileptic activity. Before describing the syndrome of infantile spasms in some detail, two other epileptic encephalopathies are briefly described to illustrate the effect of continuing subclinical and clinical epileptic activity on the cognitive development in childhood.

1.1.1.3.1. The Landau-Kleffner-Syndrome

The strongest evidence for subclinical epileptic activity causing an encephalopapthy comes from a later onset EE, the acquired epilepsy-aphasia syndrome (also called the Landau-Kleffner Syndrome). This epilepsy syndrome usually presents between 3 and 7 years of age (Neville *et al.,* 2006) and is characterized by an acquired aphasia, paroxysmal EEG

abnormalities, seizures and the absence of a focal brain lesion (Deonna *et al.,* 1995). The onset of this acquired epileptic aphasia is variable, most often subacute, or progressive and with spontaneous fluctuations (Deonna *et al.,* 1995). The type of aphasia seen is typically a verbal auditory agnosia (Rapin *et al.,* 1977) but all types of aphasia can occur (Chevrie-Mueller *et al.,* 1991). Additional impairments may include attention deficit/ hyperactivity, motor organization problems and features of autistic spectrum disorder (Neville *et al.,* 1998; Neville *et al.,* 2000). Approximately seventy percent of patients present with seizures, which are generally easily controlled (Neville *et al.,* 2006). However EEG findings are by definition consistently abnormal in LKS, regardless of the occurrence of seizures (Beaumanoir, 1992). Most common are centrotemporoparietal discharges consisting of slow waves, spikes and spike-wave discharges (Beaumanoir, 1992). In most patients with LKS these epileptiform abnormalities increase during sleep amounting to continuous spike and wave pattern occupying between 50-85% of slow wave sleep (CSWS). In the thirty percent of patients without clinical seizures at presentation, the language and cognitive impairment may be explained on the basis of these continuous subclinical high rates of discharges in sleep (Beaumanoir, 1992). The continuous subclinical discharges may also be associated with atrophic changes in the temporal lobes. The superior temporal areas (planum temporale and superior temporal areas) in children with Landau-Kleffner Syndrome were smaller compared to children with partial focal seizures. None of the patients within the study had frequent seizures, but all had very active epileptiform activity (three out of four patients had the EEG pattern continuous spike-wave in slow wave sleep) which may have caused the atrophic changes of the temporal lobes (Takeoka *et al.,* 2004), but currently no longitudinal data exist. While the continuous epileptiform activity may cause structural damage to the temporal lobes, it could also cause functional damage by affecting the processing of language. Auditory long latency evoked responses time-locked to the interictal spikes were associated with a greater reduction in amplitude and increase in latency over the left hemisphere than over the right hemisphere (Seri *et al.,* 1998).

The frequency and type of seizures do not affect the outcome and the prognosis and outcome of LKS are very unpredictable (Loonen *et al.,* 1990; Beaumanoir, 1992). An early onset before five years of age, persisting temporal EEG abnormalities and the duration in terms of years of CSWS seem to be associated with an unfavourable outcome (Tassinari *et al.,* 2002).

1.1.1.3.2. Gelastic seizures in association with hypothalamic hamartoma

Gelastic seizures are characterised by frequent, repeated attacks of unnatural mirthless laughter (Kerrigan *et al.,* 2005). If gelastic seizures are associated with a hypothalamic hamartoma they may provide a further model of an epileptic encephalopathy, although "hypothalamic gelastic epilepsy" is not recognized as a separate syndrome in the ILAE classification of 2001 (Engel, 2001). Nevertheless the association between hypothalamic hamartoma, precocious puberty and gelastic seizures is well established (Deonna *et al.,* 2000). This form of epilepsy, often refractory to conventional AEDs, appears to be extremely rare, is characterised by sudden episodes of inappropriate laughter and a peak seizure frequency at around 2-3 years of age. Most children have an arrest in their development with major behavioural problems coinciding with the onset of epilepsy (Deonna *et al.,* 2000). Out of 67 cases, 52 were reported to be cognitively and behaviourally abnormal, but no details of the cognitive and behavioural problems were given (Deonna *et al.,* 2000). There is evidence from invasive monitoring that the hamartoma is the origin of the gelastic seizures with secondary spread to the frontal and temporal cortex (Munari *et al.,* 1995). Therefore, the acquired cognitive arrest and behavioural symptoms in these children are most likely to result from the direct effect of seizure activity, because children with hypothalamic hamartomas and precocious puberty, but without seizures, do not present cognitive and behavioural problems (Stewart *et al.,* 1998).

1.1.2. The encephalopathy of infantile spasms/West syndrome

1.1.2.1. Incidence, onset and clinical presentation of infantile spasms

The most common early onset EE is the syndrome of infantile spasms (IS) or West syndrome, which has an estimated incidence at between 0.25 and 0.60 per 1000 live births per year. The reported prevalence rate ranges from 0.14 to 0.52 per 1000 children, with an average of 0.25 per 1000 children (Hrachovy *et al.,* 2003). IS show a strong age dependence and begin almost exclusively during the first year of life, with a maximum incidence between 3 and 7 months of age. This age related encephalopathy combines paroxysmal events of different types of spasms (spasms in clusters), psychomotor deterioration and diffuse and nearly continuous paroxysmal activity in the EEG, with hypsarrhythmia being the most characteristic pattern. The term West Syndrome is synonymous with IS and recalls the original description of IS by Dr William West in his own son in 1841(West, 1840). More boys are affected than girls. The range of aetiologies associated with IS is large and includes neurocutaneous syndromes, brain malformations and various diffuse, prenatal or acquired encephalopathies (Watanabe, 1998). As a general rule any early process affecting brain development can cause IS. An important cause is tuberous sclerosis (Pampiglione *et al.,* 1975; Hunt, 1983; Curatolo *et al.,* 2001) in which IS are common and where outcome in those with early onset spasms is usually poor, with global developmental delay and autistic features seen in 60 % (Shepherd *et al.,* 1995).

Infantile spasms are traditionally divided into cases of symptomatic origin versus those of non-symptomatic (cryptogenic) origin. Patients with normal prior development, no known causal factors and those with normal imaging may be categorized as cryptogenic ("hidden lesions"). In the past, the number of reported patients with cryptogenic designation has ranged from as low as 6% to as high as 66% (Hrachovy *et al.,* 2003). These differences are heavily dependent on the extent of the investigations performed and improvement in diagnostic imaging techniques. Although IS are frequently associated with poor neurodevelopmental outcome, it has been suggested that there is a truly idiopathic form

with normal outcome (Dulac *et al.,* 1993; Vigevano *et al.,* 1993). This idiopathic group may be recognized at the onset as these infants show no mental regression, preserved visual behaviour, absence of focal interictal EEG abnormality after intravenous diazepam and reappearance of hypsarrhythmia between consecutive spasms of a cluster (Dulac *et al.,* 1993). However, predicting normal outcome using ictal EEG characteristics was not confirmed by Haga and colleagues, who found no significant difference between patients with persistence or reappearance of hypsarrhythmia and the patients without hypsarrhythmia between episodes of spasms. On the contrary several patients with IS without hypsarrhythmia re-occurring between spasms had a good outcome (Haga *et al.,* 1995). The pathophysiological mechanisms generating the possible reappearance of hypsarrhythmia are not known. Therefore, the criteria by Dulac *et al* (1993) have not been widely replicated and further work in this area is required before the findings can be reliably translated into clinical practice. In this study we will only differentiate between symptomatic and cryptogenic patients.

1.1.2.2. Diagnosis and current methods of assessment

The diagnosis of the syndrome of IS is based upon the clinical history and examination, supported by neurophysiological data. Characteristic spasms and an abnormal EEG are essential for the diagnosis. There may be abnormal development prior to the onset of spasms, regression with continuing spasms but in a small group development both before the onset of spasms and during the course of the spasms remains normal. Recommended initial investigations include an EEG, skin examination including ultraviolet light for possible hypopigmented skin patches in tuberous sclerosis and magnetic resonance imaging (MRI) of the brain. As metabolic and acute infections are uncommon causes for IS further metabolic investigations and cerebrospinal fluid analysis are usually carried out as a second stage if there is sufficient clinical suspicion of such an underlying pathology and if other investigations are normal. Ophthalmologic examination may in rare cases suggest the underlying aetiology, as for example in Aicardi syndrome and in congenital infections. A

retrospective study examining the effectiveness of using such a stepwise diagnostic evaluation for infantile spasms supports the above approach (Trasmonte *et al.,* 1998).

1.1.2.2.1. Seizures

IS (Kellaway *et al.,* 1979b; Dulac *et al.,* 1994) are characterised by sudden bilateral symmetrical contraction of muscles of the neck, trunk and extremities. The type of seizure depends on whether the flexor or extensor muscles are predominantly affected and on the extent of the contraction. Mixed flexor/extensor spasms, accounting for 50 % of the cases, are the most common type. These consist either of flexion of the neck, trunk and elbows with knee extension or, less commonly, of flexion at the hips with knee extension and elbow extension with varying degrees of flexion of the neck and trunk and are dependent on the child's resting position when the spasms supervened. Spasms may be also asymmetrical, and these are often associated with a symptomatic aetiology in particular with unilateral lesions, although such lesions may also be associated with symmetrical attacks. The spasms occur in repetitive series (clusters) in which each attack is brief, lasting only seconds and occurring at intervals of 5-40 seconds. Infants may have ten to hundreds of spasms daily and the number of spasms is often vastly in excess of what parents report (Kellaway *et al.,* 1979a; Gaily *et al.,* 2001). The repetitive character of the spasms is a very important diagnostic clue. A cry is common at the time of, or just after each spasm. In young infants, atypical presentations (head nodding, eye elevation, movement of one limb) occurring repetitively might be the only clue to the diagnosis of infantile spasms. A variety of clinical phenomena such as respiratory rate changes, abnormal eye movements (nystagmus, eye opening or closing), smiling and grimacing have been reported to occur in association with the spasms. Clusters may occur in sleep, but tend to occur more frequently at the time of awakening or at the transition from slow to REM sleep (Plouin *et al.,* 1987). Clusters are also frequent during drowsiness. They are not precipitated by any obvious stimulus (Plouin *et al.,* 1987).

1.1.2.2.2. EEG

The most common EEG pattern observed in children with IS is hypsarrhythmia (Cowan *et al.,* 1991; Jeavons *et al.,* 1992), although this is not the sole EEG finding. Gibbs and Gibbs (1952) defined hypsarrhythmia as an EEG consisting of "very high voltage, random, slow waves and spikes in all cortical areas (Gibbs *et al.,* 1952).The spikes vary from moment to moment in duration and location, at times they seem to be focal in one part of the cortex, and a few seconds later they seem to come from another focus, or possibly from multiple foci. The chaotic appearance of this abnormality gives the impression of a nearly total disorganization of cortical voltage regulation". Overall 40-70 % of children show hypsarrhythmia, but in patients with tuberous sclerosis and infantile spasms only 22 % showed hypsarrhythmia (Gomez *et al.,* 1999).

In many patients atypical forms of hypsarrhythmia are seen (Hrachovy *et al.,* 1984). One of the more common variants is asymmetrical hypsarrhythmia, which refers to a hypsarrhythmic EEG in which there are consistent voltage asymmetries between the two sides. This may be associated with underlying structural abnormalities of the brain (Hrachovy *et al.,* 1984; Watanabe *et al.,* 1993). The interictal pattern of hypsarrhythmia is seen more frequently in NREM sleep than in wakefulness or arousal. In REM sleep hypsarrhythmia is not observed. The continuity of the paroxysmal discharges also changes with states of awareness and is greatest in wakefulness and stage 1 but decreases with stage 2-3 (Watanabe *et al.,* 1993).

Several attempts have been made to correlate the severity of hypsarrhythmia with outcome (Rating *et al.,* 1987; Kramer *et al.,* 1997). It has been suggested that a favourable outcome is associated with the classical symmetrical hypsarrhythmia evolving to either both focal epileptogenic activity or symmetrical sleep spindles or to a normal EEG. By contrast a grossly asymmetric hypsarrhythmia is associated with poor outcome (Saltik *et al.,* 2002). Different scoring protocols for the severity of hypsarrhythmia, failure to distinguish

between findings in sleep and wakefulness, failure to distinguish findings before or after treatment and imprecise descriptions of cognitive outcome make comparison of the published studies difficult. Therefore no scoring protocol has been adopted for routine clinical assessment in individual patients.

The ictal EEG pattern corresponding to spasms is variable (Kellaway *et al.,* 1979c). The most characteristic ictal EEG patterns are a positive wave over the vertex-central region, spindle–like medium amplitude fast activity and diffuse flattening called decremental activity (Fusco *et al.,* 1993). Correlating clinical manifestations and ictal EEG in 36 patient's video-EEG and polygraphic recordings showed the slow wave to be always present and corresponding to the clincal spasms. The fast activity occurred either alone or was followed by the slow wave and never corresponded to a clinical spasms. When there was only fast activity, the main clinical feature associated was a motionless stare and this tended to occur either at the beginning or the end of a cluster. The decremental activity was rare and always followed the slow wave and clinical spasms, but was never accompanied by clear behavioural events (Fusco *et al.,* 1993). The reported frequency of fast beta activity was 17.5 Hz (Panzica *et al.,* 1999) preceding a cluster of spasms or 14-16 Hz (Fusco *et al.,* 1993) at the end of a cluster of spasms. The reported frequency within the gamma band was 50-100 Hz during the middle part of a cluster of spasms (Kobayashi *et al.,* 2004).

1.1.2.2.3. Mental Deterioration

Mental deterioration may precede, coincide with, or follow the onset of spasms (Gastaut et al ., 1964b, Jeavons and Bower , 1964). In a small number of children, cognitive development may remain normal (Jeavons *et al.,* 1973). In many children there is a definite behavioural regression that occurs in previously well infants, with regression of vocal production and loss of visual interest. The infants may not turn their head towards visual stimuli and lack visual responsiveness. There may be a complete loss of social communication. They may no longer take notice of people and lose responsive smiling.

Loss of eye tracking and smiling in infants with IS appear to be prognostic indicators of the poor mental outcome seen in most children (Dulac *et al.,* 1993; Jambaque *et al.,* 1993). A prospective study in children with perinatal brain injury showed that most of those who subsequently developed West syndrome lost previously acquired visual and cognitive abilities. Abnormal visual attentiveness was still present after the acute phase of the syndrome at the age of 2 years (Guzzetta *et al.,* 2002). Motor regression is usually less profound, but voluntary reaching and grasping often disappear (O'Donohoe, 1985).

1.1.2.3. Outcome

The prognosis for IS is poor with cognitive impairment in 71-90% of children and a mortality of between 5 and 30% (Riikonen, 1996; Trevathan *et al.,* 1999; Wong *et al.,* 2001). In 30% to 50 % of patients visual, auditory and motor deficits are present in the long-term outcome (Pollack *et al.,* 1979; Riikonen, 1982). Psychiatric disorders are diagnosed in approximately 28% of children (Riikonen, 1984), with autistic spectrum disorder and attention deficit hyperactivity disorder being equally represented. Other seizure types and syndromes follow infantile spasms in 50 to 60% of children. These include complex partial seizures and the Lennox-Gastaut syndrome, which are the most common forms (Riikonen *et al.,* 1981; Riikonen, 1982). Unfavorable prognostic factors include a symptomatic aetiology, onset earlier than 3 months (Jeavons *et al.,* 1973a) and the presence of other types of seizures before the spasms. A better prognosis is associated with the absence of these factors and also mild or absent mental deterioration at the onset of therapy (Jeavons *et al.,* 1973a).

1.1.2.4. Treatment

Infantile spasms are difficult to treat and usually resistant to conventional antiepileptic drugs. Corticosteroids, ACTH, vigabatrin (VGB), sodium valproate, benzodiazepines and pyridoxine have been found to be effective in seizure control in a proportion of cases, but even after successful treatment children are commonly left with severe developmental

delay. The mode of action of these drugs remains unknown. Most studies are retrospective and there is a paucity of prospective studies and even fewer randomised or controlled treatment trials. The American Academy of Neurology and the Child Neurology Society, reviewing the medical treatment for infantile spasms, concluded that ACTH is probably effective for the short-term treatment of infantile spasms and resolution of hypsarrhythmia, but there is insufficient evidence to determine its optimum dosage and duration of treatment (Mackay *et al.*, 2004). A meta-analysis of the literature concerning treatment of infantile spasms concluded that the optimum treatment remains uncertain (Hancock *et al.*, 2003). Only ten randomised controlled trials (RCTS) were found at that time. Of these studies none showed any drug to be more efficacious than any other in terms of long-term psychomotor development or subsequent epilepsy rates. Recommended first line treatments for infantile spasms also differ from country to country. In the United States ACTH (Bobele *et al.*, 1994) is the first-line agent, while in Japan pyridoxine followed by valproate and ACTH (Ito *et al.*, 2000) are the first-line agents. In the 1990s, Vigabatrin (VGB) was introduced in Europe as an effective treatment for infantile spasms, particularly in tuberous sclerosis (Aicardi *et al.*, 1996). The United Kingdom Infantile Spasms Study (UKISS) results comparing VGB (150mg/kg per day) with prednisolone (40 mg per day) or intramuscular tetracosactide (0.5mg) on alternate days in a multicentre, randomised controlled trial have shown that hypsarrhythmia resolved in more infants on hormonal treatments (81%) than on Vigabatrin (56%). The primary outcome was cessation of spasms on days 13 and 14. Cessation of spasms was more likely in infants given hormonal treatments (73%) than those given VGB (54%). There was no difference in outcome between the two hormonal treatments. 21 (70%) infants responded to prednisolone and 19 (76%) to tetracosactide (Lux *et al.*, 2004). Response to treatment was also not affected by the underlying aetiology. Infants with tuberous sclerosis were not included in the UKISS study, given their assessment of the existing data of a good response to VGB in infants with IS and TS. In a follow up study absence of spasms at 14 months of age was similar in each treatment group. The neurodevelopment score using the Vineland adaptive behaviour scales (VABS) on an

intention treat basis did not differ significantly between hormone or vigabatrin treatment. In infants with IS and no identified underlying aetiology the mean VABS score was higher in infants being treated with hormones than in those allocated VGB (Lux *et al.*, 2005). Only one small study evaluated the cognitive long-term effect outcome in children with IS and TS treated with VGB in which the cessation of spasms with VGB was associated with a significant improvement in cognition and behaviour, including recovery from autistic behaviour (Jambaque *et al.*, 2000). Although Vigabatrin is generally well tolerated, there is evidence of irreversible concentric visual field defects in 30-50% of patients of all ages treated with VGB (Gross-Tsur *et al.*, 2000; Vanhatalo *et al.*, 2002). Although this side effect of VGB is worrying, in the context of intractable seizures or the encephalopathy of infantile spasms, the therapeutic benefits must be weighed against the risks.

The effect of short tem treatment on long-term outcome was outside the purpose of this study. The medical treatment of IS was rigorously assessed in a review by Mackay et al 2002 using class I, II and III evidence according to the American Academy of Neurology. The object of their review was to subject established empirical medical treatment regimens for infantile spasms to evidence-based medicine analysis in order to determine the current best practice for the treatment of infantile spasms in children. There was no strong evidence that successful treatment of infantile spasms improves the long-term prognosis for cognitive outcome or decreases the incidence of later epilepsy.

1.1.2.5. Current knowledge about causes for cognitive outcome in infantile spasms

The cause of the bad cognitive outcome in infantile spasms is unknown. A current concept is that the interictal EEG activity may be the primary cause for cognitive impairment as hypothesised for the Landau-Kleffner syndrome and CSWS (Dulac, 2001; Holmes, 2002). Whilst the mechanisms for the poor neurodevelopmental outcome in children with IS are unknown, there is growing evidence that the mechanism for the poor outcome may be

related to functionally abnormal temporal lobes during a critical phase of development (Bolton et al., 1997; Asano et al., 2001; Bolton et al., 2002).

1.1.2.5.1. Evidence for functionally abnormal temporal lobes

Social cognition includes information processing about all people, including the self and about the norms and the procedures of the social world (Beer and Ochsner 2006). A unique human component of social cognition, which is the ability to explain and predict other people's behaviour by attributing to them different independent mental states, such as beliefs and desires , is known as having a "theory of mind (ToM)".

Through lesions studies in primates, imaging studies, including fMRI, PET and MEG experiments social cognition has been associated with essential brain regions of the temporal and frontal lobes.

The temporal lobe involves regions including the extrastriate body area of the posterior temporal cortex (association with perceiving the form of other bodies (Saxe et al 2004), posterior superior temporal sulcus (association with interpreting the motions of a human body in terms of goals, Saxe et al., 2004, Ramnani et al., 2004), the temporoparietal junction supporting the human ability to reason about the contents of mental states (Saxe et al., 2003) and the temporal poles (critical for aspects of face processing, specifically recognition from auditory and visual clues). Subregions of the medial prefrontal cortex are also implicated in the processing of social cognition. While the ventral medial prefrontal cortex appears to support emotional empathy (Blair 2005), the dorsal medial cortex is implicated in representing shared or collaborative attention and goals; being triadic relations between me, you and this (Tomasello et al., 2005).

There is evidence that children with autism have a lack of social cognition and ToM (Hill EL et al., 2003), which may explain the failures of communication and social interaction.

While temporal regions implicated in social perception, language and theory of mind abilities may be impaired in autism, the temporal lobe may also be functional abnormal in epileptic EEs. The evidence comes from the Landau-Kleffner (LKS) syndrome, which is the classical example of subclinical seizure activity and centro-temporal epileptic discharges in sleep associated with cognitive and language impairment (Section 1.1.1.3.1).

Temporal lobe focal abnormalities were seen in seventy-three out of two hundred and fourteen children with infantile spasms in a long-term follow-up study. The temporal lobe was significantly more affected in children with autistic or hyperkinetic behaviour and in children with neonatal hypoglycaemia (Riikonen, 1982).

In addition the late appearances of a temporal lobe focus in many children following IS have been confirmed by systematic EEG studies (Riikonen, 1982). Temporal lobe focal abnormalities were seen in seventy-three out of two hundred and fourteen children with infantile spasms in a long-term follow-up study. The temporal lobe was significantly more affected in children with autistic or hyperkinetic behaviour and in children with neonatal hypoglycaemia (Riikonen, 1982). Patients with structural lesions and evidence of epileptic discharges in the temporal lobe may also have a poor neurodevelopmental outcome and autistic spectrum disorder (Raymond *et al.,* 1994; Neville *et al.,* 1997; Gomez *et al.,* 1999; Taylor *et al.,* 1999). Structural evidence for temporal lobe involvement arises from the finding that tubers and developmental tumours within the temporal lobe, are strong predictors of an autistic spectrum disorder (Raymond *et al.,* 1994; Taylor *et al.,* 1999). The association between tuberous sclerosis and autism or atypical autism has also been related to the presence of tubers in the temporal lobes, the risk of mental retardation increased with an increasing number of tubers (Bolton *et al.,* 1997). Patients with tuberous sclerosis are at high risk of developing an autism spectrum disorder when temporal lobe tubers are associated with temporal lobe epileptiform discharges and early-onset, persistent spasms-like seizures (Bolton *et al.,* 2002). This risk was less if seizures started in the second year of

life. There is also an association between cognitive and behavioural impairments in children with dysembryoplastic neuroepithelial tumours (DNT) presenting with epilepsy, especially when the lesions involved the temporal lobe. Of the children with DNT, the most severely regressed, with prominent autistic features, frequently had right temporal lesions and the onset of epilepsy in the first year of life (Neville *et al.,* 1997; Taylor *et al.,* 1999). There is further evidence from Fluoro-D-Glucose positron emission tomography (PET) and electrophysiological studies, that children with autistic spectrum disorder associated with IS have dysfunctional temporal lobes. Children with tuberous sclerosis and a history of infantile spasms are more likely to have a communication disorder if they have glucose hypometabolism in the lateral temporal gyri (Asano *et al.,* 2001). In a study of 17 infants with cryptogenic infantile spasms, cortical hypometabolism was detected in 11 infants on the first PET and in five infants on the second PET. The rate of developmental delay at the last follow-up was significantly higher in infants with hypometabolism than in those without PET abnormalities. In these children the temporal region was always involved in the area of focal hypometabolism (Itomi *et al.,* 2002). Chugani and colleagues also documented hypometabolism most commonly in the parieto-occipito-temporal region and the outcome was especially poor in infants having bilateral temporal hypometabolism (Chugani *et al.,* 1996). There is also electrophysiological evidence of a deficit in auditory information processing and automatic memory in children with TS having the autistic spectrum disorder compared to children with TS (Seri *et al.,* 1999).

Therefore we hypothesize that the temporal lobe is functionally abnormal in children with infantile spasms and that this occurs early in the course of the syndrome. The auditory processing system is part of temporal lobe function and can be investigated with auditory event related potentials (ERPs), which may be recorded in infants independently of arousal and attention. We used therefore auditory ERPs to assess the temporal lobe function in infants with infantile spasms.

1.2. The central auditory system and event related potentials

1.2.1 The anatomy of the temporal lobe and the neuroanatomy of the central auditory system

The lateral region supports auditory function (primary, secondary and association auditory cortex), speech and the integration of information arriving from sensory association areas. The integrated information is distributed to other brain regions for emotional (ventromedial lobe), cognitive (frontal association area) or motor (basal ganglia) processing for elaboration or response preparation. The ventromedial region of the temporal lobe contains the limbic system with the parahippocampal gyrus, the entorhinal cortex, the hippocampal formation, the uncus, the amygdale and the cortex of the temporal pole (Martin 1996).

Once an auditory impulse has been generated in the cochlea the signal travels along the auditory nerve to the cochlear nuclei. From there projections lead to the contralateral inferior colliculus via the lateral lemniscus while other projections undergo an additional stage of processing at the superior olivary nuclei. The superior olivary nuclei are involved in sound localization and binaural processing. The axons of the olivary neurones do also project to the homolateral inferior colliculus via the lateral lemniscus. The neurons of the inferior colliculi project via the brachium of the inferior colliculus to the medial geniculate body, which then projects via the auditory radiation to the primary auditory cortex contained in the transverse temporal gyri of Heschl (Musiek *et al.,* 1986; Musiek, 1986a; Musiek, 1986b).

Our knowledge of the anatomical and functional organization of the human auditory cortical system comes largely from studies in non-human primates using microelectrode recordings, tracer studies and histochemical analyses. The anatomical and neurophsiological findings in monkeys support the idea of multiple, parallel streams of processing in the primate auditory system involving temporal, parietal and frontal cortices. Functional

neuroimaging evidence indicates that a similar organisation might underlie human auditory system (Scott *et al.,* 2003).

The auditory information is relayed from the ventral nucleus of the medial geniculate complex (MGv) to three primary areas of auditory cortex ("core") (Figure 1.1), which project callosally to the auditory core of the other cerebral hemisphere and also to the surrounding "belt" (Figure 1.2) composed of several different cortical areas. These "belt" areas are connected to "parabelt" areas (Figure 1.3). These areas are distinguished from each other by having different systematic representations of the cochlea (cochleotopic organization) and their responses to different pure tones/frequencies (tonotopic organization, Figure 1.1). There is evidence of at least three levels of auditory processing in a hierarchical manner from MGv→ core→ belt→ parabelt (Figures 1.2 and 1.3). The parabelt is interconnected with adjacent portions of the temporal cortex (superior temporal gyrus and sulcus), parietal lobe and several regions of the frontal lobe. These further connections can be considered components of an additional, fourth level of auditory processing (Figure 1.3; Kaas *et al.,* 1999; Kaas *et al.,* 2000). Studies of human auditory cortex show a similar anatomical organization mapping auditory core, lateral belt and parabelt cortices in the superior temporal gyrus (Sweet *et al.,* 2005).

The auditory system shows specialized pathways for processing of acoustic signals present within the environment ("what") and to localize the direction from which these signals originate ("where"). A "what" stream involves rostral belt and parabelt, which are connected with the anterior superior temporal gyrus and sulcus and multiple sites within the ventrolateral and dorsolateral frontal cortex (Figures 1.4 and 1.5). A "where" stream for sound localisation involves the caudal auditory belt and parabelt, which are connected with the posterior superior temporal gyrus and sulcus, parietal cortex, ventrolateral and dorsolateral cortex (Figures 1.4 and 1.5).

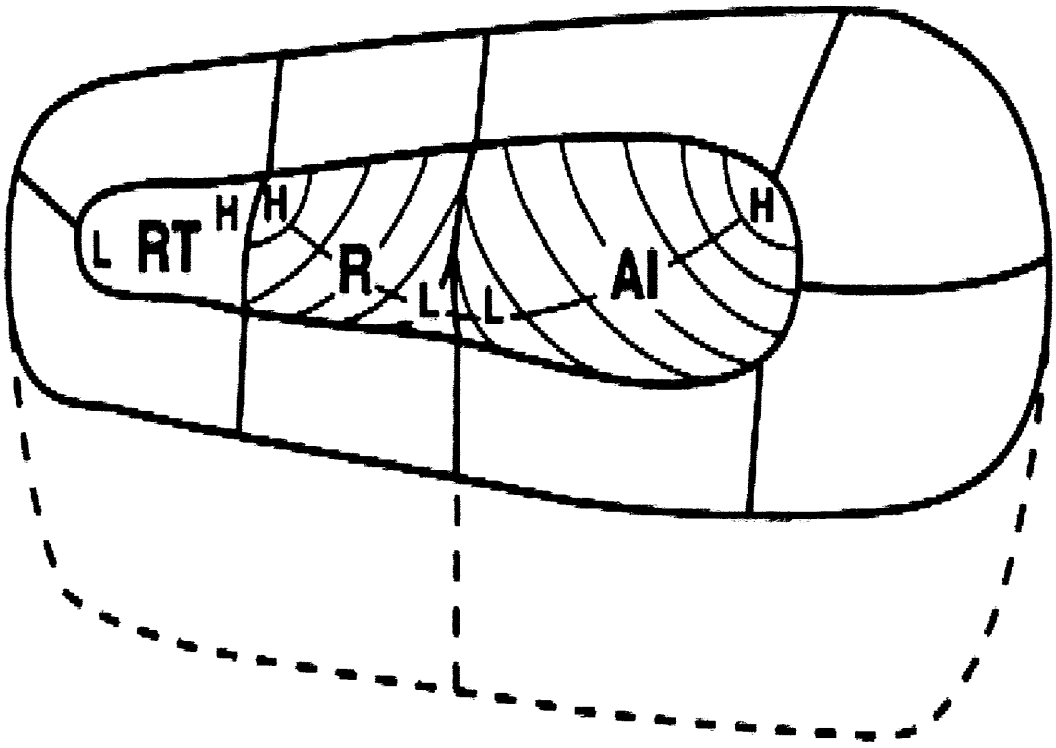

Figure 1.1. Tonotopic organization in the auditory core of the monkey. Auditory core fields (AI, R, RT) are surrounded by belt fields (not labeled).

Curved lines within each field depict isofrequency contours. High- (H) frequency acoustic stimuli are represented caudomedially in AI, rostromedially in R. Low- (L) frequency stimuli are represented rostrolaterally in AI, caudolaterally in R. Tonotopic organization in RT is not as certain but may mirror that found in R (Kaas *et al.*, 2000).

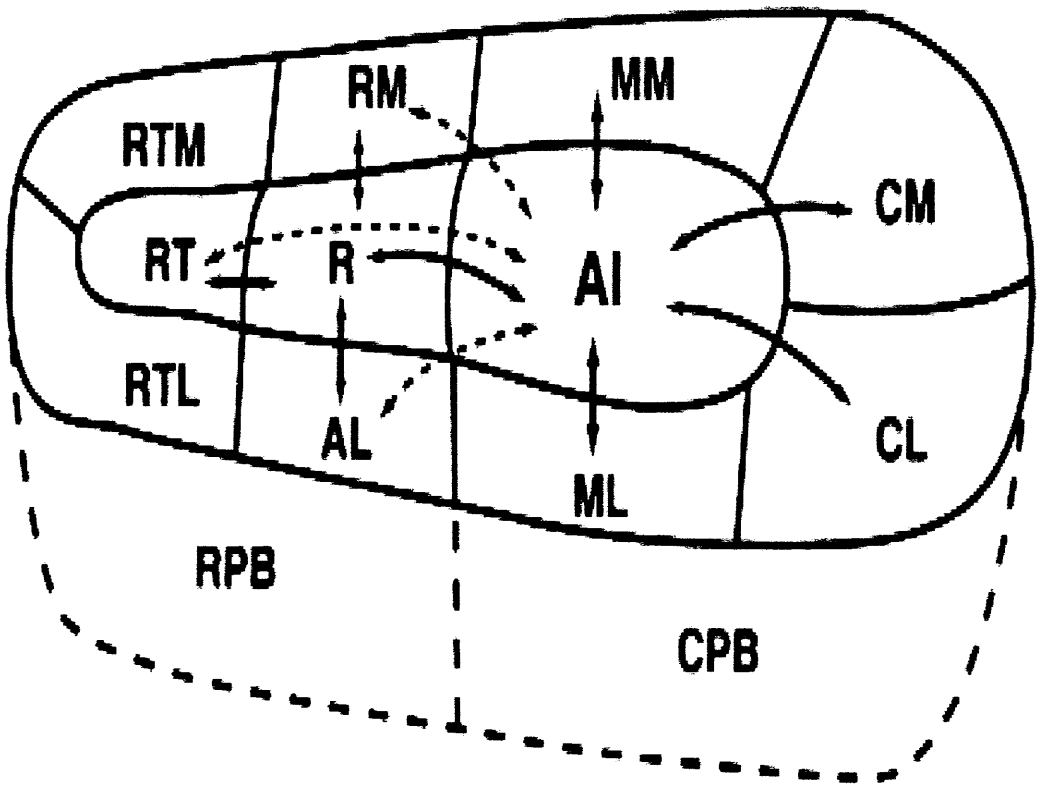

Figure 1.2. Auditory cortical connections of the primary auditory cortex (AI) in the monkey.

Area AI, as well as other core areas, has dense reciprocal connections with adjacent areas of the core and belt (solid lines with arrows). Connections with nonadjacent fields are less dense (dashed lines with arrows). The core has few, if any, connections with the parabelt or more distant cortex (Kaas *et al.*, 2000).

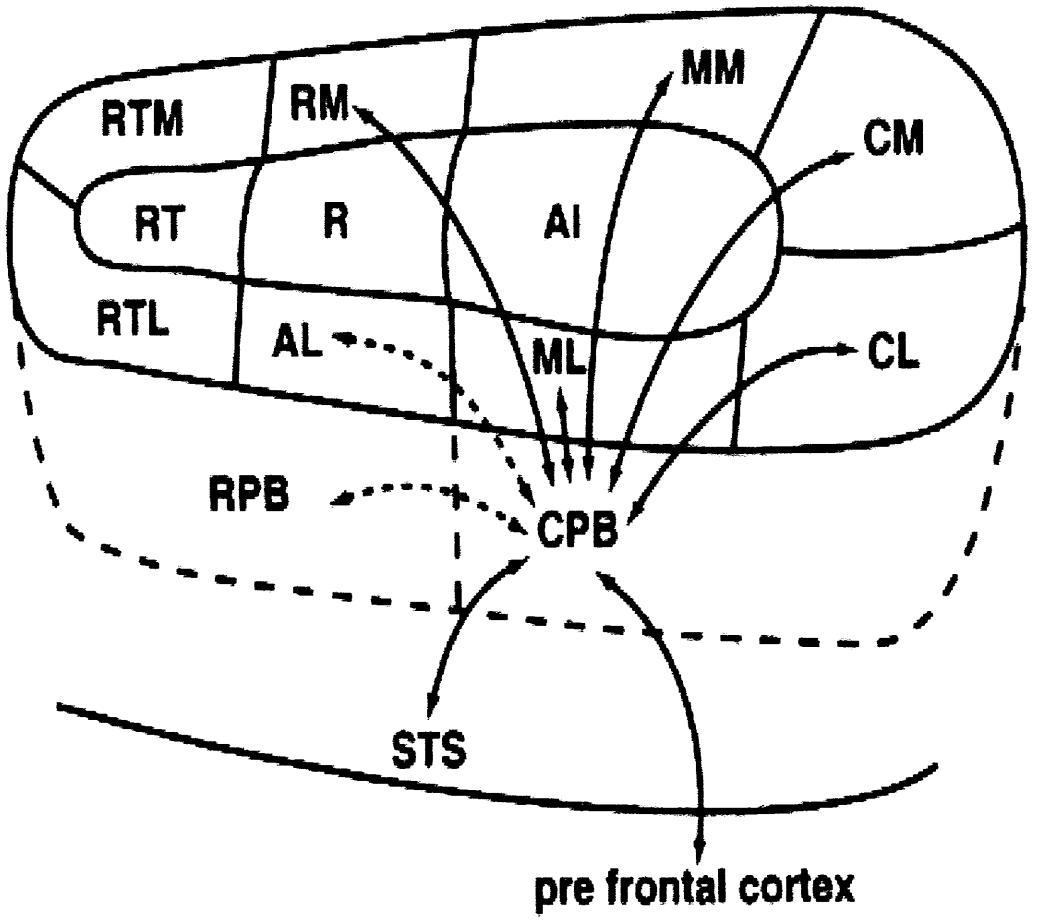

Figure1.3. Auditory cortical connections of the caudal parabelt (CPB) in the auditory cortex of the monkey.

Parabelt area CPB, as well as RPB, has dense connections with adjacent areas of the belt and RM in the medial belt (solid lines with arrows). Connections with nonadjacent fields of the belt tend to be less dense (dashed lines with arrows). The parabelt fields have few, if any, connections with the core areas. The parabelt also has connections with the polysensory areas in the superior temporal sulcus (STS) and with functionally distinct fields in prefrontal cortex (Kaas *et al.*, 2000).

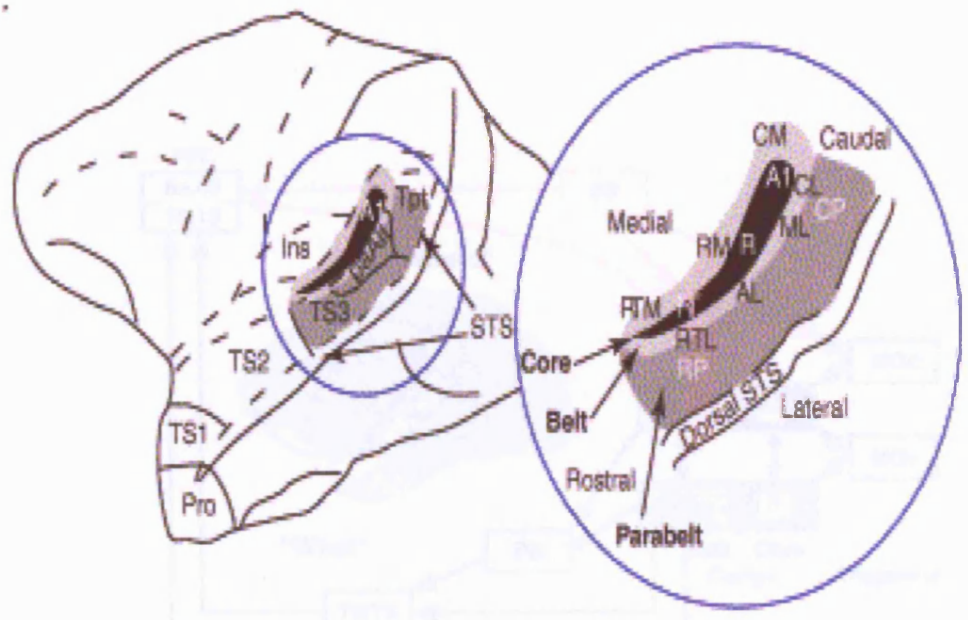

Figure1.4. Specialization in the primate temporal lobe. Inset shows the supra-temporal plane in greater detail.

Abbreviations for figure 1 to 4: AI, auditory area I; R, rostral area; RT; rostrotemporal area; CL, caudolateral area; CM, caudomedial area; ML, middle lateral area; RM, rostromedial area; AL, anterolateral area; RTL, lateral rostrotemporal area; RTM, medial rostrotemporal area; CPB, caudal parabelt; RPB, rostral parabelt (Scott *et al.*, 2003).

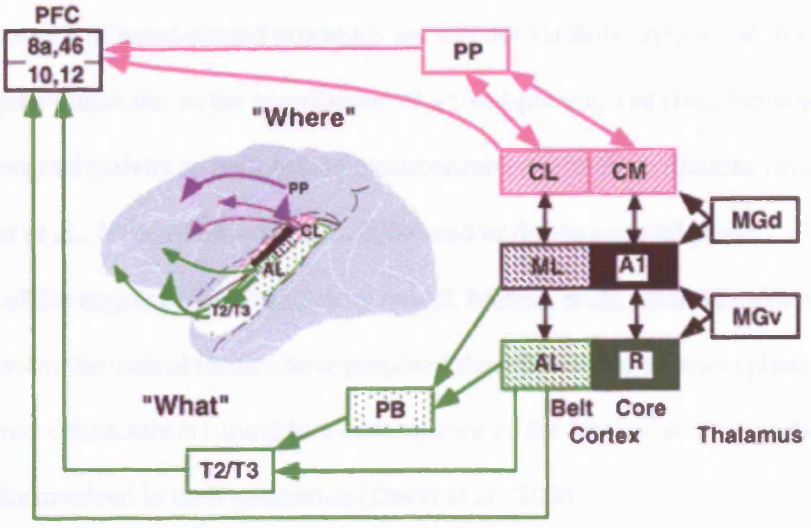

Figure 1.5. Schematic flow diagram of "what" and "where" streams in the auditory cortical system of primates.

The ventral "what"-stream is shown in green, the dorsal "where"-stream, in red. A1 primary auditory cortex; R, rostral area; CM, caudomedial area; AL, anterolateral area; ML, middle lateral; CL, caudolateral; PP posterior parietal cortex; PB, parabelt cortex; MGd and MGv, dorsal and ventral parts of the MGN (medial geniculate nucleus), T2/T3 (anterior pole of the temporal lobe).

(Rauschecker *et al.*, 2000).

1.2.2. Electrophysiological indices of the auditory system function

Electrophysiological responses to sound can be measured non-invasively, objectively and precisely by using auditory evoked potentials (AEPs). These are the electrical responses of the nervous system to sound, recorded on the surface of the scalp. The mechanisms involved in the genesis of event-related potentials are still not yet fully understood. It is not known whether ERPs arise due to the contribution of a fixed-polarity and fixed latency superimposed neuronal activity to background electroencephalograhic oscillations (evoked model, Schroeder et al., 1995, Maekinen et al., 2004) and/or due to a partial phase synchronization of the ongoing EEG (oscillatory model, Makeig et al., 2002, Kruglikov and Schiff, 2003). Recent theoretical studies have proposed that ERP characteristics (phase resetting and power enhancement) could be a consequence of the level of activity of the neuronal networks involved in their generation (David et al., 2005).

Scalp-recorded cortical AEPs are principally a reflection of post-synaptic dendritic potentials (Luck, 2005). The interface through which they interact with surrounding neurons usually consists of several dendrites (input connections), which are connected via synapses to other neurons, and one axon (output connection). If the sum of the input signals surpasses a certain threshold, the neuron sends an action potential (AP) at the axon hillock and transmits this electrical signal along the axon. Neurons of a particular functional area such as the primary auditory cortex will tend to fire together if the stimulus is sufficient. These neurons are extensively connected both to each other and other neuronal groups. The neurons which will fire depend on the characteristics of the input and of its processing. This notion of interconnected groups of neurons selectively involved in specific functions is called a neuronal network

If an excitatory neurotransmitter is released at the apical dendrites of a cortical pyramidal cell, current will flow from the extracellular space into the cell around the apical dentrites, and currents flow out of the cell body and basal dentritites at more distal sites, creating a dipolar source –sink configuration oriented perpendicular to the cortical sheet. The opposite

happens if the distal parts of the dendrites are activated. As hundreds of thousands of such cells are activated, a summated potential may be detected on the surface of the scalp (Kuta *et al.,* 1997). The (usually scalp-recorded) average of all the cellular sources and sinks can be summarised as an "equivalent dipole". The summated potential on the scalp is only observable on the scalp if the average distribution of positive ("sources") and negative ("sinks") potentials in the neurons are distributed in a non-radially symmetric fashion and the neurons are aligned systematically and are activated synchronously (Figures 1.6 and 1.7; Kuta *et al.,* 1997). The neocortex of the brain fulfils these criteria above. Around 70% of the cells in the neocortex are pyramidal cells having apical dendrites extending from their soma towards the surface of the sheet, giving the cortex a columnar appearance.

Human AEPs are generally divided into auditory brain stem responses (ABR), middle-latency responses (MLR) and long-latency responses (Figure 1.8). Auditory brain stem responses seen within the first 10ms after the stimulus are widely used clinically to assess auditory sensitivity and to detect abnormalities of peripheral and brainstem portions of the auditory pathways (Biacabe *et al.,* 2001). Middle latency potentials (MLR) occur 10-80ms after an acoustic stimulus and are also characterised by several components (Liegeois-Chauvel *et al.,* 1994). MLR may be detected in children during wakefulness and sleep stages 1, 2 and REM, but less during stage 4 (Kraus *et al.,* 1989, Kraus *et al.,* 1995). Longer latency potentials (>80ms) are thought to reflect higher auditory cortical processing as discussed below.

1.2.3. Time and phase-locked auditory potentials

Auditory evoked potentials are small and therefore are usually masked by the background activity (noise) of the EEG and individual responses cannot be distinguished. The technique of signal averaging serves to extract the responses, which are time-locked to the stimulus, from unrelated potential changes. Ideally the repeated presentation of an identical stimulus will evoke to the same potential (signal) waveform. By collecting and adding each response

to the preceding one, the underlying evoked potential will remain unchanged and the random noise will tend to average out (towards zero). A computer with an analog-to-digital converter carries out averaging, records the continuous voltage changes during selected time intervals (epochs), adds the responses of multiple epochs and divides them finally by the number of trials to arrive at a mean for each epoch and displays the waveform on the screen. The relationship between the signal to noise ratio (SNR) and the number of responses is not linear: the SNR improves by the square root of the number of responses that are averaged (Luck, 2005). It may be therefore difficult to average the signal out of the very abnormal background EEG noise as seen in infants with IS, which will be considered further below.

1.2.3.1. Event-related potentials

The long-latency potentials are also called event related potentials (ERP), which can be divided into exogenous and endogenous potentials in any one modality (Donchin *et al.,* 1978). Exogenous, or obligatory, ERP components are elicited by the occurrence of a stimulus in the particular modality under consideration. They are determined by the physical stimulus characteristics and change their properties only in relation to stimulus features. In contrast, endogenous components do not obligatorily depend on the external stimuli (Naatanen, 1992). They show a greater variability in comparison to the exogenous components. They are thought to reflect mainly internally generated mental events related to the cognitive assessment of the stimulus. According to Donchin *et al* (1978) endogenous components must be non obligatory responses to stimuli. "Amplitude, latency and scalp distribution of the endogenous potential are often invariant to changes in the physical parameters of the eliciting stimulus. Quite disparate stimuli, even stimuli in different modalities elicit the same components if their task–roles are equivalent. The variance of endogenous components is normally accounted for by variation in the tasks assigned to the subject". The exogenous-endogenous distinction is nevertheless an oversimplification of the real state of affairs. Almost all sensory early components have been shown to be modifiable

by attention and the later cognitive components have been shown to be influenced by the modality of the stimulus. Thus those ERP components occurring within the first 100-200 ms tend to be more exogenous, while those occurring later tend to be more endogenous (Rugg *et al.,* 1996).

1.2.3.1.1. Exogenous (obligatory) auditory ERPs

1.2.3.1.1.1. Obligatory auditory ERPs in adults and school-age children

The first obligatory component of long latency auditory ERPs in adults is a positive deflection P1, sometimes also called P50, peaking around 50 ms. When recording evoked potentials from the auditory cortex in man the generator of the P 50 was found to lie in the lateral portion of the Heschl's gyrus (HG), i.e. the primary auditory cortex (Liegeois-Chauvel *et al.,* 1994). The second component, the first negative component, is the N1 response peaking around 100 ms. This peak is composed of multiple, partly temporally overlapping, independent components observed at the vertex and over lateral temporal electrode sites (Naatanen *et al.,* 1987). The first component, the vertex N1 has a fronto-central negativity with a peak latency of 100ms and is generated by bilateral vertically oriented dipoles on the supratemporal planes of the auditory cortices (Vaughan *et al.,* 1970) including secondary auditory cortex lateral to the HG. The second component of the N1, first described by Wolpaw and Penry (1975) who called it the "T complex", is biphasic and has a positive peak at around 80 ms and a negative one at around 130 ms. This complex originates in the auditory association cortices in the superior temporal gyri (secondary auditory cortices) and can be modelled by bilateral radially oriented dipoles (Picton *et al.,* 1999). The third component is a vertex-negative wave with a latency of 100 ms, generated in modality non-specific areas (Naatanen *et al.,* 1987). The components N1a and N1c refer to the positive and negative components of the T-complex respectively and N1b refers to the vertex N1 (Giard *et al.,* 1994).

The N1 component is followed by a second positive polarity, P2, with a latency of approximately 150-250 ms. The topography of the P2 appears to be similar across auditory, visual and somatosensory modalities, being maximal over the vertex (Oades *et al.,* 1995; Potts *et al.,* 1998). Using magnetoencephalography (MEG) and EEG data P2 generators were localized in the planum temporale as well as area 22 (the auditory association complex), (Godey *et al.,* 2001).The localisation of P2 in area 22 was only found using the MEG data, but this finding is consistent with the MEG data by Hari *et al* (1987), locating the generator anterior to the generators of the N1 peak. Further studies indicate that the P2 reflects at least partly auditorly driven output of the mesencephalic reticular activating system, which responds to input from all sensory modalities (Knight *et al.,* 1980; Naatanen *et al.,* 1987; Rif *et al.,* 1991, Woods *et al.,* 1993; Crowley *et al.,* 2004).

The P2 is followed by a pronounced second negativity, N2, which has an adult latency of 220-270ms (Ponton *et al.,* 2000). It has been suggested that the N2 has bilateral generators in the supratemporal auditory cortex (Gomot *et al.,* 2000; Ceponiene *et al.,* 2002b). The N2 generation in 5-11–year-old children might also have additional frontal and parietal cortical fields involved (Gomot *et al.,* 2000). The N2 is a component, which has mainly been reported in children, but it has also been recorded in adults, but with a smaller amplitude (Ponton *et al.,* 2000) and in some reports longer latency (Ponton *et al.,* 2000). The N2 amplitude in children is largely insensitive to stimulus rate, but changes as a function of the stimulus content (Ceponiene *et al.,* 1998).The N2 was larger in response to complex rather than simple tones and to low pitched rather than high-pitched tones.

1.2.3.1.1.2. Maturation of obligatory auditory ERPs during infancy

In previous studies of infant ERPs a predominant positive deflection at about 300 ms has most commonly been labelled as P2 and a later negative deflection at about 500-600ms as N2, but the labelling between laboratories varied and the infantile peaks did not correspond to the adult peaks with the same labels. Differences in nomenclature, recording montages,

stimuli, interstimulus-intervals and waking state makes a comparison between these studies very difficult (Table 1.1). Most of these studies showed increasing peak amplitudes with age and shortening of latencies. Peak amplitudes did not increase linearly. Vaughan *et al* (1992) showed an inverted-U function at 6 months, but this was not shown by other studies (Ohlrich *et al.,* 1972; Shucard *et al.,* 1987a; Shucard *et al.,* 1988). Latencies of ERP peaks generally decreased with development; however Shucard *et al* (1987) found an increasing latency within the first 3 months. Cortical auditory ERPs recorded longitudinally from birth until 12 month of age at 3-monthly intervals, showed 4 components labelled as P150, N250, P350 and N450 (Kushnerenko *et al.,* 2002a). 5 awake infants were recorded monthly between 3 and 24 months of age by (Jing *et al.,* 2006). The latencies of the P150, N250, P350 and N450 components gradually decreased with increasing age. The amplitudes of the N250 and P350 components gradually increased and reached a maximum at 9 months of age and then gradually decreased with increasing age.

1.2.3.1.2. Endogenous discriminative components of the auditory ERP

The endogenous components can be elicited in the oddball paradigm where infrequent stimuli ("deviants") are embedded in a series of repetitive identical ("standard ") stimuli. These deviant stimuli differ from the standards in one or more characteristics. Oddball paradigms may be used during recordings in which the subject is either actively paying attention or not. During the active recording the subject's task is to react with a motor response or just by silently counting a particular class of target (deviant) stimuli embedded into a sequence of otherwise irrelevant non-target stimuli. If not actively paying attention, the subject is asked to ignore all the stimuli and sometimes asking the subject to read a book or to watch a silent video reinforces this. Because infants and young children are unable to follow an instruction to actively attend to the stimulus, ERP paradigms in this age group are regarded as passive. The endogenous components occurring after 100-200ms from stimulus onset require no mental activity on part of the participant for their evocation. Among the

endogenous components elicited in the oddball paradigm and described further on are the MMN, the P3a and the late negativity (Nc), which are passively elicited.

1.2.3.1.2.1. The Mismatch-Negativity

The mismatch-negativity (MMN) has an adult latency between 100 and 250ms from change onset. Presenting the subject with a block of several hundred identical stimuli ("standards"), which are occasionally replaced by acoustically deviant stimuli, and thereafter subtracting the response elicited by standards from that elicited by the deviants elicits the MMN (Naatanen *et al.,* 1995). This neural mismatch process between a deviant sensory input and the neural representation or sensory memory trace formed by the repetitive standard sounds appears to be automatic since the MMN is elicited even by changes in unattended auditory stimuli. In adults the largest amplitudes of the MMN are recorded over the fronto-central scalp. MEG studies and intracranial recordings have found major generators bilaterally in the auditory cortices. Although the MMN may be demonstrated reliably during adulthood (Naatanen *et al.,* 1995), it is not found consistently during infancy (Morr *et al.,* 2002). There is a great intersubject variability of the MMN in latency and amplitude of the MMN in the same infants from birth to 1 year of age at a 3-month follow-up study. A MMN present at birth may be absent at 3 months of age in the same normal developing infant. There was also no significant decrease of the MMN latency with age during the first year of life (Kushnerenko *et al.* 2002b). Finding the MMN in normal developing infants may be difficult, but demonstrating it in infants with a very abnormal EEG and an anticipated very low signal to noise ratio may be impossible. This was also part of the investigation reported in this thesis.

1.2.3.1.2.2. The P3a

Novelty detection is a fundamental capacity of all mammalian nervous systems (Sokolov, 1963). The ability to orient to novel, unexpected or unpredictable events is critical for both survival (Sokolov, 1963) and normal memory function (Von Restorff, 1933). The use of a

novelty oddball paradigm (low-probability novel stimuli in addition to target and standard stimuli) demonstrated that involuntary orientation to an unexpected and novel stimulus generated a P300 response, recorded between 250-350ms post stimulus onset (Courchesne *et al.,* 1975; Squires *et al.,* 1975). This Novelty P300, also referred to as P3a response, may be elicited both by attended and unattended stimuli and habituates across successive presentations of novel items. Although some P300 responses have been elicited by simple stimuli and labelled as novelty responses the P3a is most clearly elicited by stimuli which are unexpected in the context set by the standard stimulus (Squires *et al.,* 1975; Simons *et al.,* 2001). It has to be distinguished from the P3b response, which is generated by voluntary detection of a task-relevant event, by a shorter peak latency, smaller amplitude and a different (fronto-central vs centro-parietal) scalp topography (Sutton *et al.,* 1965). Both the P3a and P3b have been observed in all sensory modalities (Knight, 1984; Knight, 1996). The prefrontal cortex and the medial temporal lobes are important components of the network generating the novelty P3.

Intracranial recordings of patients with epilepsy have shown that novel stimuli activate a distributed network including the bilateral dorsolateral, ventrolateral, and orbital prefrontal cortex, cingulate cortex, lateral temporoparietal cortex, hippocampus and parahippocampal cortical regions (Figure 1.9, Halgren *et al.,* 1995a; Halgren *et al.,* 1995b; Baudena *et al.,* 1995). Patients with focal brain lesions involving either lateral prefrontal, lateral temporoparietal or posterior medial temporal regions have also shown attenuated novelty P3 responses in all modalities (Figure 1.10, Ranganath et al 2003).

The ability to detect and respond to novel stimuli in the environment is especially important in infants and young children as they have to process many novel events. Developmental studies showed a decreasing latency of the novelty P3 and a more frontal topography between the ages of 5-16 years (Cycowicz *et al.,* 1996; Cycowicz *et al.,* 1997). In adults and children (7-13 years) an early- (eP3a; peak latency 200-250ms) and a late component (lP3a; peak latency 250-350 ms) of the P3a have also been identified (Escera *et al.,* 1998; Gumenyuk *et al.,* 2001). In adulthood characteristics of the early component are maximal

amplitude over the fronto-central scalp and polarity inversion over the lateral and posterior scalp sites. By contrast, the IP3a is maximal frontally, distributed more anteriorly to the eP3a and does not show an inverting polarity over the posterior scalp (Escera *et al.,* 1998). There is currently no systematic study of auditory novelty ERP during infancy. (Kushnerenko *et al.,* 2002b) reported pilot data on novelty ERP in six newborns and six 2 year olds, without specifying the state of arousal during recording. Newborns, which were presented with an auditory oddball paradigm including novel environmental sounds, showed a different distribution and ERP waveform in response to novel than to the deviant stimuli during quiet sleep. This may suggest that the auditory detection mechanism for novelty is already present in the newborn period (Sambeth *et al.,* 2006).

1.2.3.1.2.3. Late negativities in attended conditions

The late negativity component (Nc) with a peak latency of about 300-1000 msec and fronto-central distribution scalp distribution may be regarded as a sign of enhanced auditory and visual selective attention, since it was elicited in response to surprising, interesting stimuli. The amplitude of the Nc is maximal during childhood, and decreases during adulthood (Courchesne, 1990). Recording auditory stimuli in 9-13 years old children and using left and right mastoid electrodes as a reference two components of the Nc following each other may be differentiated. The first component (Nc1) had a peak latency of 400-750ms and was followed by a second component (Nc2) at a latency of 800-1100ms (Ceponiene *et al.,* 2004). It is therefore reasonable to suggest that the frontal predominance of the early portion of Nc has at least some of its generator sources residing in the frontal lobe (Ceponiene *et al.,* 2004).

1.2.4. Influence of sleep on auditory ERP recordings

In the newborn period, physiological measures other than EEG parameters such as EMG tone, phasic twitches, rapid eye movements and respiratory regularity are the most useful features to differentiate between wakefulness, non-rapid eye movement (NREM) sleep and

rapid eye movement (REM) sleep (Anders, 1971). In the first few months of life NREM is classified as quiet sleep and REM as active sleep. Quiet sleep is conventionally differentiated into four sleep stages. Stage 1 is characterised by bursts of high-voltage, rhythmic theta activity, sleep stage 2 by sleep spindles and K complexes and stages 3 and 4 contain slow, high-voltage delta waves (also called slow-wave sleep or delta sleep). Stages 2, 3 and 4 EEG patterns occur only in NREM sleep state, whereas the stage 1 EEG pattern can occur in wakefulness, REM sleep and NREM sleep (Anders, 1971). During sleep, REM and NREM states alternate and follow each other in a periodic fashion and compose together a sleep cycle (Anders, 1971). This alternating REM/NREM organization is seen by 4 months of life (Kahn *et al.,* 1996).While the amount of quiet sleep increases with age, active sleep decreases. Quiet sleep is the dominant sleep phase in 60% of infants at 3 months and in 90% of 6-month-old-infants, when the proportion of quiet sleep is twice that of active sleep (Kahn *et al.,* 1996).

Auditory ERPs of newborns do not appear to differ significantly from each other when obtained during active sleep or wakefulness (Ellingson *et al.,* 1974; Kurtzberg *et al.,* 1984). Although there has been no systematic study in infancy or childhood reproducing this finding, this result has been used by several authors as justification for not distinguishing between findings in active sleep and wakefulness in their analysis. ERP studies in adults indicate that auditory information processing is selectively affected across the different stages of sleep (Atienza *et al.,* 2001). The processing of external auditory stimuli is markedly reduced during stages 3 and 4 and rapid eye movement sleep (REM) (Ogilvie *et al.,* 1988). There is currently no systematic evidence suggesting how auditory processing in infancy is affected by wakefulness and sleep. Stage 2 seems to be ideal to study having been identified as the most reliably and easily recognizable EEG pattern on having entered definite sleep (De Gennaro *et al.,* 2001). This issue is also addressed in the current study.

1.3. Aims of the present studies

Based on the aforementioned evidence (Section 1.1.2.4.1) that the temporal lobes are important in normal cognitive development and the evidence of temporal lobe involvement in the encephalopathy of IS, the hypothesis of this study is that the temporal lobes are functionally abnormal in infants with infantile spasms. Auditory long latency ERPs are thought to reflect higher auditory cortical processing and were therefore used in this study to support or refute this hypothesis. In order to test this hypothesis a major part of this study was also to study the ERPs in normal developing babies.

1.3.1. Primary Aims

1.3.1.1. Are obligatory and novelty auditory ERP components measurable in infants with IS within the first 14 months of life in the context of a very abnormal EEG?

1.3.1.2. Are obligatory and novelty auditory ERP components measurable in normal developing infants within the first 14 months of life and do they show any latency/ amplitude changes with increasing age?

1.3.1.3. Are obligatory and novelty auditory ERP components in IS abnormal compared to control infants?

1.3.1.4. Have age of seizure onset, response to treatment (seizure control after 2 weeks), development before the onset of spasms either being normal or delayed, abnormal MRI (symptomatic)/normal MRI (cryptogenic) a predictive value on initial ERP ?

1.3.2. Secondary Aims

1.3.2.1. Are there differences in auditory ERP components between waking and sleep state in infants with IS compared to control infants?

1.3.2.2. Are the infantile ERP peaks analogous to any childhood or adulthood peaks?

CHAPTER 2: METHODOLOGY

2.1. Ethical considerations

The Research Ethics Committee of Great Ormond Street Hospital for Children (GOSH) and the Institute of Child Health (UCL) approved this study. The parents gave informed consent after reading an information leaflet (Appendix 1 and 2).

2.2. Participants

2.2.1. Controls

Thirty two healthy, normally developing infants aged 1-15 months were recruited through nurses and doctors at Great Ormond Street Hospital, UCL-Institute of Child Health, the National Centre for Young People with Epilepsy and some university colleagues. Criteria for normality were age-appropriate development and the absence of familial congenital hearing impairment, chronic otitis media or other significant health problems as obtained by parental interview.

2.2.2. Infants with infantile spasms

Thirty-four infants with infantile spasms aged 1-15 months were recruited from newly referred patients, the tuberous sclerosis clinic and the epilepsy programme at GOSH. Consultant paediatricians working in District General Hospitals were informed about the study by letter and by personal contact. They were encouraged to refer any newly diagnosed patients. Several educational talks for middle grade training and consultant staff were given at district general hospitals by Professor Neville and myself to raise awareness of this study and of the importance of infantile spasms. Inclusion criteria were clinical infantile spasms

and an abnormal EEG compatible with IS with or without hypsarrhythmia. Infants with other seizure types, but without infantile spasms, were excluded from this study.

2.2.2.1. Clinical and developmental assessment of infants with infantile spasms

All infants with infantile spasms were seen within 1 week of referral. The patients were seen by the candidate and a consultant paediatric neurologist who decided about investigations and treatment. The data including age of onset, description of the first seizure and of IS, response to treatment within 2 weeks with standard medication, history of development prior to onset of IS, observed developmental delay during IS, electroencephalogram, metabolic investigations and any indications of a possible underlying diagnosis including tuberous sclerosis, cortical malformation or a syndrome were prospectively obtained and later extracted from the notes using a standardized form (Appendix 3). The examination of IS included a developmental screening appropriate for age including fine motor and vision, gross motor, hearing and speech and social behaviour and play (Flehmig, 1992). Infants were categorized as normal or abnormal. In addition to the candidate and consultant, Dr Tim Cox, consultant neuroradiologist, at Great Ormond Street Hospital independently reviewed the magnetic resonance imaging scans of all patients for possible underlying structural brain abnormalities to arrive at a consensus diagnosis.

2.3. Instrumentation

The equipment for the acquisition of ERPs consisted of 2 systems. Auditory stimuli (Section 2.4.3) were delivered through a sound card in a PC. These stimuli were amplified using a Cambridge A1Mark2 audio amplifier and played at an intensity of 75 dB sound-pressure levels (SPL) via two speakers placed at a distance of 30 cm from each ear of the infant. The EEG montage had 19 channels (Section 2.4.1). EEG signals were recorded and digitised at 500 Hz using 'SYNAMPS' amplifiers and 'Neuroscan version 4.2' software

(Neurosoft Inc, Herndon VA) running on a second PC, which controlled the display and storage to a hard disk for subsequent off-line analysis.

2.4. EEG and recording procedure

2.4.1. EEG

The EEG was recorded with a band pass filter of 0.15-100 Hz. Silver/silver-chloride electrodes were attached using adhesive paste according to the international 10-20 system at Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, Pz, P3, P4, T5, T6, and left and right mastoids (M1, M2). All were referenced to CPz. The ground electrode was placed on Fp1. Input impedance was kept below 10 kOhm.

2.4.1.1. EEG in infants with infantile spasms

Dr Stewart Boyd, consultant in paediatric clinical neurophysiology, who was blinded to the underlying pathology in the individual patient, independently examined the degree of EEG abnormality.

The following EEG criteria were assessed using these definitions:

1. Moderate abnormality

Unequivocal excess of slow activity of similar amplitude to the on-going activity, present for less then 50 % of the recording, with definite evidence of age–appropriate activity.

2. Severe abnormality

Continuous excess of slow activity and /or absence of age–appropriate rhythmic activity and frequent epileptiform features.

3. Hypsarrhythmia

The EEG abnormalities consist of diffuse, high amplitude, a non-synchronous paroxysmal and slow wave theta and delta activity with loss of background features that is continuous when awake and fragmented in sleep. This hypsarrhythmic pattern may be symmetrical or asymmetrical because of additional foci, or unilateral.

4. Exacerbation of EEG abnormalities by sleep

Since EEG abnormalities may be more disorganized and of higher amplitude in sleep this variable was analysed separately (Section 1.1.2.2.2)

5. Persistent focal changes

The EEG had no focal discharges, multifocal discharges or L or R hemisphere focal discharges.

6. Ictal recordings of Infantile spasms

There are no specific ictal patterns associated with infantile spasms (Section 1.1.2.2.2). If infantile spasms were documented during the recording, the changes were categorized as:

1a. Isolated transient lasting around 0.5s, positive at the vertex

1b. This (1a) could be followed by an electrodecremental period (an abrupt reduction in the amplitude of all activities lasting more than 1s, with disappearance of theta and delta activities) of up to 4sec,which in turn might or might not contain runs of more rhythmic activity.

2. A burst of faster components (12-20 ms): lateralisation was noted if present.

3. Other changes including bursts of spike-wave complexes.

2.4.1.2. Sleep staging

EEG criteria for awake/drowsiness were presence of muscle activity and/or hypnagogic hypersynchrony (high amplitude rhythmic theta activity of drowsiness in infants, (Hughes, 1994). Stage 2 sleep state was defined by the presence of sleep spindles, variable degree of irregular high amplitude slow delta activity (Rechtschaffen *et al.,* 1968). In infants with infantile spasms the absence of muscle activity and some organisation of epileptic activities into bursts was classified as stage II sleep, if sleep spindles were not also present (Section 1.1.2.2.2, Watanabe *et al.* 1993; Mori *et al.* 1994).

2.4.2. Recording Procedure

Infants were tested in a sound-attenuated room during periods of wakefulness and sleep. Feeding, and recordings around midday encouraged infants to sleep on their mother's lap. During wakefulness infants were engaged by their mothers. The recording session lasted between one and two hours. Recordings of ERP during wakefulness took place before and during feeding, while sleep ERP recordings took place after feeding. EEG criteria were used to define the onset of sleep (Section 2.4.1.2).

2.4.3. Experimental stimulation/oddball paradigm

The oddball paradigm stimulation consisted of frequent standard stimuli (sinusoidal tones, 1kHz, 200 ms long with 10 ms rise and fall time, probability of occurrence p=80%) and infrequent deviants (1.5 kHz, 200 ms long, p=10%), and infrequent novel sounds (p=10%). Brief environmental sounds (mechanical and animal noises, musical instrument sounds etc., maximum duration 200ms, peak intensity less than 75 dB SPL) served as novel stimuli. A pseudo-random sequence was used in all recordings (Appendix 4). Stimulus onset asynchrony (SOA) was 700 ms. A stimulus block contained 923 stimuli (including 747 standards, 88 deviants and 88 novels) and, whenever possible, 2 blocks were recorded during both wakefulness and sleep respectively.

2.5. Data processing

Continuous EEG data were referenced to a common average reference. EEGs were reviewed off-line for movement and other major artefacts. The recordings of controls and patients were categorized into sleep and wake states on the basis of the predominant (more than 60%) EEG pattern (Section 2.4.1.2). ERP epochs were then constructed with 200 ms pre- and 1800 ms post-stimulus periods and baseline correction was applied to the -200 ms to 0 ms interval. The data were artefact rejected using an automated procedure with a specific amplitude threshold and visually inspected to eliminate clipped signals (amplifier saturation). As in other studies, epochs exceeding +/- 150 μV in the awake state (Cheour *et al.*, 1998; Cheour *et al.*, 2002) and +/- 250 μV in stage II sleep were automatically rejected before the averaging process in the control infants. There is no literature on recording similar auditory ERPs in infants or children with epilepsy and EEGs with high amplitude on-going activities. Infants with IS have a background with variable high amplitude of EEG activities (Section 1.1.2.2.2, Table 3.13). It was therefore not possible to use the same amplitude criteria as in normal controls. The rejection criteria for each of the infants with IS were therefore set with reference to the abnormal background activity of the EEG and the calculated signal to noise ratio.

2.6. Signal to noise ratio (SNR) considerations

An adverse SNR was anticipated in infants with IS. The duration of the recording was limited by the infant's tolerance, the family's commitments, the need to replicate responses to each stimulus and the need to record in two states. An SNR of 2 was therefore selected as a practicable compromise provided the ERP component was identifiable in multiple neighbouring electrodes as well as being replicable in at least 2 separate consecutive recordings. In conjunction with the paediatric neurophysiologist Stewart Boyd the average amplitude of background activity ("noise") of the EEG during both wakefulness and sleep, excluding large amplitude spikes and waves, was estimated as an average amplitude from baseline by visual inspection in each individual patient with IS. The estimated background

activity in each patient with IS was compared with the peak to peak amplitude of the novelty or obligatory "signal" measured in normal infants. The SNR ratio improves with the square root of the numbers of epochs averaged (Section 1.2.3.). The necessary averages to obtain a SNR of 2 may therefore be calculated in wakefulness and sleep.

2.7. Measurement of ERP components

The peak latency of components was identified by visual inspection of the waveforms, and measured with an electronic cursor. The amplitude of components was measured from baseline to peak of sequential components. As noted above, the component had to be clearly visible across multiple neighbouring electrodes and replicable in at least two consecutive blocks in the same state of arousal.

2.7.1. Obligatory ERP

Obligatory ERPs to frequent standard tones were re-referenced to the mean of both mastoid electrodes M1 and M2 and low pass filtered at 10 Hz for comparison with previous reports (Kushnerenko *et al.,* 2002a). Measurements were taken at a positive peak (P150) followed by a negative (N250) and a further positive peak (P350) at electrodes F3, Fz, F4, C3, Cz and C4 in wakefulness and sleep (Figure 2.1).

2.7.2. Mismatch-Negativity

All electrodes were re-referenced to the mean of both mastoid electrodes M1 and M2. The MMN waves were obtained by subtracting the response to the last standard stimulus from that before a deviant stimulus, high pass filtered at 1Hz and low pass filtered at10 Hz. The MMN was defined as the largest negative deflection in the difference waveform between 80 and 300ms after stimulus onset, greater than the average baseline voltage by 1.0 μV at any two of the four-central electrodes (F3, F4, C3 and C4).

2.7.3. Novelty ERP

Negative components over bilateral inferior temporal and mastoid electrodes (labelled N250) and positive components over the fronto-frontolateral-central region (labelled P250F, P250FL and P250C) were measured. The early P250 (eP250), the late P250 (lP250), early N250 (eN250) and late N250 (lN250) components were measured at F3, F4, C3, C4 and mastoid (M1, M2) and inferior temporal (P7, P8) electrodes. Long-latency negative waves (labelled Nc1 and Nc2) were measured over the fronto-central midline (F3, F4) and more prominently with longer latencies over dorso-lateral frontal regions (F7, F8). Positive slow components (P500) were measured in bilateral mastoid and inferior temporal leads (Figure 2.2).

Sleep specific central negative components (labelled NcS) were measured at central electrodes C3, C4 and Cz (Figure 2.3). To improve the detection of peak amplitudes and latencies for novelty ERPs, signals were low pass filtered with a 10 Hz zero-phase digital filter (slope 6 dB).

2.8. Analysis with reference to the primary and secondary aims

In order to analyse the IS data, the first step was to compare group mean averages of ERP waveforms in normal developing infants within the first 14 months of life (Section 1.3.1). Averages were constructed in three age groups (1-4, 5-8 and 9-14 months) to investigate whether obligatory, MMN and novelty auditory ERP components are measurable and whether the latencies change with increasing age. Afterwards the latencies and amplitudes of the obligatory, MMN and novelty ERPs of the three age groups were compared.

As a second step group mean averages of ERP waveforms were compared by constructing group averages across the same groups (1-4, 5-8 and 9-14 months) in infants with IS to investigate whether obligatory, MMN and novelty auditory ERPs are measurable (Section 1.3.1.1). These group mean averages were then visually compared to the group averages

recorded in normal controls to investigate whether infants with IS show differences in their auditory ERPs. If infants had not already been investigated and examined at the referring hospitals they were investigated at GOS including an EEG, MRI head scan and if appropriate a metabolic (infectious) workup for an underlying metabolic or infectious aetiology (Appendix 3). Professor Brian Neville or Dr Rod Scott supervised the clinical examination and investigations.

The clinical data of the patients with IS in terms of age of seizure onset, response to treatment (seizure control after 2 weeks), development before the onset of spasms either being normal or delayed, abnormal MRI (symptomatic)/normal MRI (cryptogenic) were related to initial ERPs at presentation and outcome at 2 years to assess the predictive value of these factors on initial ERP and developmental assessment outcome at 2 years (Section 1.3.1.5).

Whenever possible, recordings in infants with IS and controls were made in both wakefulness and sleep (Section 1.3.2.1). The ERP findings were analysed separately according to state. The latencies and amplitudes of the obligatory and novelty components in both states were then compared between the two groups.

It is difficult to decide whether the infantile ERP peaks can be regarded as analogous to any of the child and adult ERP peaks (Section 1.3.2.2). Some conclusions could however be made on similar stimulus paradigms and decreasing latencies of similar ERP components.

2.9. Statistics

SPSS version 11 (Chicago, Illinois) was used for all the statistical analyses. A repeated measures ANOVA was used to assess the effect of age upon latencies and amplitudes of various components of the ERPs effects after adjustment for hemisphere, state of awareness and gender in the control subjects. The ERP components investigated were the P150, N250, P350, fP250, flP250, N250, P500, Nc1, Nc2 and NcS.

As data were not normally distributed, non-parametric ANCOVA correlations were carried out, when comparing the control subjects and the children with infantile spasms. after adjustment for age. Differences in ERP components in children with infantile spasms compared to control subjects, after adjustment for age were investigated.
Spearman correlation coefficients were used in the investigation of relationships between ERP latencies and clinical factors such as normal or abnormal development before seizure onset, normal or abnormal development at outcome at 2 years of age normal or abnormal MRI brain scans and EEG abnormalities such as presence of hypsarrythmia, moderate or severe EEG abnormality, persistent focal changes, exacerbation of EEG abnormalities by sleep and ictal recordings of infantile spasms.

For data reduction purposes the following ERP components were averaged separately for latency and amplitude as following: P150 at electrodes F3, F4, C3 and C4; N250 at electrodes F3, F4, C3 and C4; P350 at electrodes F3, F4, C3 and C4; fP250 (P2a) at electrodes F3, F4 and Fz; flP250 (P2b) at electrodes F7 and F8; N2 at electrodes M1, M2, P7, P8, C3, C4, and Cz; P500 at electrodes M1, M2, P7and P8; Nc1 at electrodes F3, F4 and Fz; Nc2 at electrodes F7 and F8 and NcS at electrodes C3, C4 and Cz.

In order to investigate the relationships between any ERP component being identified, the SNR and the presence or absence of infantile spasms logistic regression analyses were carried out.

CHAPTER 3: RESULTS

3.1. ERPs in Control infants

Thirty-two healthy infants including 14 boys (170 +/–90 days) and 18 girls (251 +/–111days) were recruited.

3.1.1. Mismatch-Negativity (MMN)

MMNs were analysed by comparing the standard and deviant AERPs as a subtraction waveform, constructed by subtracting the standard ERP from that of the deviant ERP. The MMN had to be greater than the average baseline voltage by 1.0 μV (Section 2.7.2). The group mean average of the 5-8 months control group showed a MMN at C4 with a latency of 210ms and amplitude of –2.8μV. The MMN reversed its polarity over the right mastoid electrode and had then positive amplitude of 3.9μV (Figure 3.1). Only two individual control infants of the 5-8 months group also showed a MMN. The MMN of the two individual infants at C4 with a latency of 220ms were –1.4 and –7.6μV and 1.7μV and 13.59μV respectively at M2 (Figures 3.2 and 3.3). The high MMN amplitude of –7.6μV at C4 and 13.59μV at M2 for the second individual remain unexplained. There is no evidence that this is an artefact arising from recording or processing these data or that another component has been misidentified as the MMN in this particular case.

3.1.2. Signal to noise ratio

Before analysing the ERP data in IS with an abnormal background EEG activity a crucial first step was to determine the background EEG activity and ERP signals in normal infants during wakefulness and sleep. Together with a consultant neurophysiologist the average amplitude of background EEG activity (regarded as noise) was estimated in control infants

to be +/-30 μV during wakefulness and +/-50 μV in stage 2 sleep. Therefore in this study assuming a novelty ERP signal of 30μV (50μV in sleep) amplitude, measured from peak to peak (P-to-P) and using the formula (Section 2.6) at least 16 responses whilst being awake and 16 responses during sleep were required to achieve an SNR of 2 (Section 2.6). The P-to-P amplitude of the obligatory ERPs was of 7μV (10 μV in sleep). Therefore at least 324 responses during wakefulness and 400 in sleep were required to obtain an acceptable SNR of 2.

3.1.3. Obligatory ERP responses

3.1.3.1. ERP waveforms

In order to describe positive and negative deflections in the obligatory responses group-average ERPs to frequent standard stimuli were computed. Figures 2.1 and 3.4 show the mean group-average of 9-14, 5-8 and 1-4 months respectively in wakefulness and sleep at electrode F3. Two prominent positive peaks were observed, the first (labelled P150) was separated from the second positive peak at 350 ms (here labelled P350) by a low-amplitude negative deflection at approximately 250 ms (N250). The N250 in the 1-4 months group was not as prominent as in older groups. The P150, N250 and P350 appeared to have higher amplitudes during sleep. The topographical distribution of ERP component amplitudes P150 and P350 showed an inversion of polarity across the anterior-posterior axis (Figure 3.5). The components were replicable within and between subjects in both wakefulness and sleep. Figures 3.6 and 3.7 and figures 3.8 and 3.9 are showing the replicability of the obligatory components P150, N250 and P350 during 2 consecutive recordings at electrode F3 during wakefulness and sleep respectively.

3.1.3.2. Age dependency

With increasing age all 3 components including the P150, N250 and P350 were measured reliably and were present in 76% of infants during sleep and 84% during wakefulness (Table 3.1).

Controls (N=30)	Awake	Asleep
P 150	26/26 100 %	30/30 100 %
N 250	22/26 84 %	23/30 76 %
P 350	22/26 84 %	23/30 76 %

Table 3.1 Presence of obligatory components P150, N250 and P350 in control infants

Using a repeated measure ANOVA a possible dependence of these components on age was investigated. The latencies of the components P150 ($p<0.001$), N250 ($p<0.001$) and P350 ($p<0.001$) shortened significantly with increasing age irrespective of arousal state (Figure 3.10). There were no significant age related changes in P150, N250 and P350 amplitudes (Tables 3.2, 3.3 and 3.4).

Further analyses were carried out to determine whether the age dependency was modified by state of arousal, gender and hemispheric side the ERP was obtained from.

3.1.3.3. Effect of arousal, side and gender

The age related effects described above were influenced by state of arousal and hemisphere. P150 ($p<0.001$), N250 ($p<0.004$) and P350 ($p<0.001$) component latencies showed shorter peak latencies and P150 was of lower amplitude ($p=0.013$) during wakefulness compared to sleep (Tables 3.2, 3.3 and 3.4). Peak latencies of the P150 were consistently shorter over the right hemisphere compared to the left, independently of age and state of arousal ($p<0.031$). There were no gender differences.

3.1.4. Novelty ERP

3.1.4.1. ERP waveform during wakefulness

In order to describe positive and negative deflections in the novelty responses group-average ERPs to novel stimuli were also computed. The group mean ERP waveforms to novel sounds showed large amplitude negative components over bilateral inferior temporal and mastoid electrodes (labelled N250) with a polarity inversion over central regions (labelled P250C, Figures 2.2 and 3.11). In addition the frontal P250 components (P250F) with different topography to those above showed an inversion of their polarity over the parietal electrodes. Double peaks of the P250 and N250, the early P250 (eP250), late P250 (lP250), early N250 (eN250) and late (lN250) were seen in some individual infants at frontal (F3, F4), central (C3, C4), mastoid (M1, M2) and inferior temporal (P7, P8) electrodes respectively. The frontal eP250F inverted its polarity with the eN250 over the inferior temporal electrodes bilaterally. Figure 3.12 shows this inversion on the R hemisphere between electrodes F4 and P8. Positive slow components (P500) were seen in bilateral mastoid and inferior temporal electrodes (Figure 2.2). Further long-latency negative waves (labelled Nc1 and Nc2) were visible over the fronto-central midline and more prominently with longer latencies over dorso-lateral frontal regions (F3, F4, F7, F8) showing an inversion of the Nc1 over the parietal electrodes (Figures 2.2 and 3.13).

The components were replicable within and between the subjects during wakefulness. Figures 3.14 and 3.15 are showing the replicability of the novelty components N250 and P500 in 2 individual infants during two consecutive recordings at electrode M1 during wakefulness.

3.1.4.2. ERP waveform during sleep

Large amplitude novelty ERPs were also recorded during sleep in all age groups (Figure 2.3). The central P250 components (Figure 3.16) at central electrodes (C3, C4) and the frontal P250 components (Figure 3.17) at frontal electrodes (F3, F4) had a polarity

inversion with N250 components over inferior temporal electrodes (M1, M2) and parietal electrodes (P3, P4) respectively. In addition to the peaks identified during wakefulness (Figure 2.2) there was an inversion of polarity between a prominent negative wave (NcS), visible at the vertex and the P500 across inferior temporal, mastoid leads (Figures 2.3 and 3.18). These NcS components were also visible over C3 and C4 electrodes (Figure 2.3), but with a smaller amplitude. The sleep components Nc1 and Nc2 were visible over the electrodes F3, F4 and F7 and F8 respectively.

The components were replicable within and between the subjects. Figures 3.19 and 3.20 are showing the replicability of the novelty components N250 and P500 in 2 individual infants during two consecutive recordings at electrode M1 during sleep.

3.1.4.3. Age dependency

The latencies of the P500 ($p<0.001$), Nc1 ($p<0.001$) and Nc2 ($p<0.001$) decreased significantly with age irrespective of arousal state (Table 3.5, 3.6 and 3.7). Figure 3.21 shows the decreasing latency of the P500 at electrode M1 during both wakefulness and sleep.

Further analysis was carried out to determine whether there was an age dependency of these and other component latencies modified by state of arousal, gender and hemisphere the ERP was obtained from.

3.1.4.4. Effect of arousal, side and gender on component latencies

The latency of the P250F (Figure 3.22, $p=0.024$) component was only found to decrease with age during wakefulness (Table 3.8). The latencies of the P250F ($p=0.01$) were also shorter during wakefulness compared to sleep, but the shorter latencies were mainly seen in the 1-4 and 9-15 months ($p=0.032$, Table 3.8).

In contrast to the peak latencies of the obligatory components P150 and P350 and also the novelty component P250, the novelty ERP components P500 ($p<0.001$), Nc1 ($p<0.001$) and Nc2 ($p<0.001$) were shorter during sleep than wakefulness (Tables 3.5, 3.6 and 3.7). There were also differences in novelty ERP peak latencies between the left and right homologous electrodes, most pronounced during wakefulness: longer P500 ($p=0.005$) latencies were observed in all age groups on the left compared to the right hemisphere (Table 3.5). During sleep this significant side difference was not present ($p=0.013$, Figure 3.23).

The latencies of the Nc1 were longer on the left hemisphere independent of arousal (Table 3.6). No effects of gender or interactions of gender and age were found on any ERP component latency.

3.1.4.5. Effect of arousal, side and gender on component amplitudes

Amplitudes of all novelty ERP components tended to be larger during sleep than wakefulness. This was significant for the amplitudes of P250 ($p=0.002$), P500 ($p<0.001$) and Nc1 ($p<0.002$, Tables 3.8, 3.5, 3.6). Figure 3.24 shows the amplitudes of the late negative Nc1 waves over frontal electrodes during wakefulness and sleep.

Amplitudes of all novelty ERP components showed non-linear age-dependencies during wakefulness, significantly for P250 and N250 (Tables 3.8 and 3.9). Maximum peak amplitudes were found in the 5-8 months group compared with both the younger and older groups (Tables 3.8 and 3.9). N250-P250 peak-to-peak amplitudes were thus plotted (Figure 3.25), also showing a maximum in the 5-8 months group. There were significantly larger amplitudes over the L compared to the R hemisphere ($F(2, 23) = 5.6$, $p=0.011$). The N250 ($F(1,24)=11.1$, $p=0.003$) and P500 ($F(1,23)=4.9$, $p=0.038$) amplitudes were also significantly larger over the left side compared to right during wakefulness (Tables 3.5 and

3.9). No effects of gender or interactions of gender and age were found on any ERP component amplitude.

3.2. Infants with infantile spasms

After the analysis of the ERPs in the control infants the clinical- and ERP data of the infants with IS were analysed and compared to the normal infants.

3.2.1. Demographical data

34 infants with infantile spasms including 11 girls and 23 boys were recruited. Only 28 infants, including 18 boys (222 days +/–110 days) and 10 girls (248 days +/–96 days) were finally included as 3 patients (two male and one female infant) with inadequate recordings due to technical difficulties had to be excluded. The 3 infants excluded were recorded with electrode caps, which were repeatedly taken of by the infant. Because patients were admitted to the study as quickly as possible it was later agreed that three further patients did not have infantile spasms: one male infant who was thought to have IS was excluded when the diagnosis of Dravet syndrome was made later, two infants with TS, who had been referred to Great Ormond Street Hospital were recorded before a complete history was taken and both were excluded, as there was only a history of complex partial seizures (Table 3.10).

3.2.2. Seizure onset of infantile spasms

An early seizure onset of less than 4 months is reported to be associated with a worse developmental outcome and we determined the seizure onset of infantile spasms in each individual patient by parental interview. Fifteen patients had a seizure onset of infantile spasms at less than 120 days (4 months) of age and thirteen patients had a seizure onset after 4 months of age (Table 3.10). Before the onset of infantile spasms, 5 patients had tonic-clonic seizures and 8 had partial onset seizures.

3.2.3. Response to drug treatment

Ten patients were treated with Vigabatrin, four with corticosteroids and fourteen patients were treated with a combination of at least 2 drugs, including either Vigabatrin or steroids. Six patients had no seizures within 2 weeks of beginning of treatment and twenty-two continued to have seizures (table 3.10).

3.2.4. EEG abnormality of the research EEGs

All patients referred to GOS were already on treatment and had had already a routine EEG compatible with the diagnosis of IS before the research EEG for the auditory ERPs was recorded. 24 patients were recorded in wakefulness and sleep and 2 patients either during wakefulness or during sleep. The research EEGs showed that during wakefulness 11 patients had moderately abnormal EEG (Figure 3.26) and 15 patients had a severely abnormal EEG (Figure 3.27). Hypsarrhythmia was seen in only one patient and 3 patients had clinical spasms during wakefulness.

During sleep 9 patients had a moderately abnormal EEG (Figure 3.28) and 17 patients had a severely abnormal EEG (Figure 3.29). 4 Patients had hypsarrhythmia (Figure 3.30) and in 8 patients the EEG became more disorganized in sleep. 11 patients had no focal discharges and 7 patients had multi-focal discharges during wakefulness.

10 patients had no focal discharges and 8 patients had multi-focal discharges during sleep. 2 patients had left focal and further 2 had right focal discharges in both states of awareness (Table 3.11).

3.2.5. MRI brain scan results

One consultant paediatric neuroradiologist reviewed the MRI brain scans of 27 patients separating between cryptogenic and symptomatic aetiology (Table 3.12). One patient with trisomy 21 has had no brain scan. Eight patients were reported to have normal MRI scans.

The abnormal MRI scans included three patients with tuberous sclerosis, seven patients with cortical dysplasia (Aicardi-Syndrome, Lissencephaly, Proteus syndrome, cortical dysplasia of right inferior parietal lobule extending into the angular gyrus region, cortical dyplasia of the left occipital and posterior parietal and temporal occipital region, cortical dysplasia of the L parietal region and one patient with an abnormal L sylvian fissure) and six infants with hypoxic ischaemia changes. The lesions in these six infants included one right middle cerebral territory infarct, one periventricular leukomalacia associated with IVH grade II, one gross white matter loss and porencephaly of the right frontal lobe, one subtle basal ganglia changes and a further patient with extensive generalized hypoxic changes to the occipital lobes bilaterally. One patient showed delayed myelination and in one further patient there was absence of the corpus callosum.

3.2.6. Development before seizure onset of IS

6 infants with an onset of IS between three and four months of age and two infants with IS with an onset between 4.5 and 6 months have had age appropriate development reported by history prior to seizure onset (table 3.10). Only one of these 6 infants had an abnormal MRI head scan showing widespread cortical tubers and subependymal nodules consistent with TS and a large tuber in the R orbitofrontal region (table 3.12).

3.2.7. SNR and EEG abnormalities in infants with IS

In infants with infantile spasms the signal may have to be extracted out of a background with a high degree of diffuse slow waves, spikes and sharp waves (Niedermayer and Lopes Da Silva 1999). This abnormal background activity may consequently diminish the SNR (table 3.13).

3.2.7.1. SNR calculations during wakefulness and sleep

Taking the number of possible stimuli in a stimulus block into consideration a SNR of 2 was thought to be sufficient to extract the novelty ERP signal or obligatory ERP response.

For the majority of the patients with a background activity of up to ±75 μV during wakefulness 100 responses were required to obtain a novelty signal with a SNR of 2.0. In sleep 162 responses (background up to 150μV) were required for a SNR of 2 (Tables 3.14 and 3.15).

At least 1849 responses during wakefulness (3600 during sleep) were required to obtain the signal of the obligatory responses with an SNR of 2. In general a background activity of > 100μV (150 μV in sleep) was anticipated to yield a low SNR (Tables 3.14 and 3.15).

It was then important to show any association between the SNR and the presence or absence of ERP components.

3.2.8. Presence of obligatory components

The first obligatory component, the P150 was detected in 50 % of infants with IS in both wakefulness and sleep compared to control subjects (100 %), while all 3 components (P150, N250, P350) were seen only in 34 % (84% in control subjects) during wakefulness and during sleep 23% (76% in control subjects, Table 3.16).

3.2.9. Presence of novelty components

During sleep novel components (N250 at electrodes M1, M2, P7, P8, C3, C4, and Cz; P500 at electrodes M1, M2, P7and P8) were present in 16/26 (61%) of infants with IS compared to control subjects in 29/30 (96%), while during wakefulness novelty ERP were only present in 11/26 (42%) compared to control subjects 23/26 (88 %, Table 3.16).

3.2.10. Presence of obligatory components and SNR

After adjusting for the SNR using logistic regression controls were 5 (95% CI: 1.1 to 24.3) times more likely to have all components identified than patients with IS during wakefulness (p=0.04). 21/26 controls have all components compared to 9/25 patients. After

adjusting for the SNR during sleep there was no difference between patients and controls in terms of the proportions with all components identified (p=0.3). 23/31 controls have all components but only to 6/26 patients.

3.2.11. Presence of novelty components and SNR

After accounting for the effect of SNR, the control subjects were 4.4 (95% CI: 0.85 to 23.2) times more likely to have all novel components detected than patients with IS (p=0.08) during wakefulness. The chance of identifying all components is increased by 1.6 (0.94 to 2.7) times for every increase in SNR of 1 unit (p=0.08).

After adjusting for the effect of SNR the control subjects are 9.6 (95% CI: 0.86 to 106.7) times more likely to have all components detected than patients with infantile spasms (p=0.07) during sleep.

3.2.12. Presence or absence of ERPs during wakefulness or sleep in infants with IS dependent on the degree of EEG abnormality

There was a relationship between the presence of obligatory components and the severity of the EEG abnormality in wakefulness (p=0.005) and in sleep (p=0.004). There was also a relationship between presence of novelty components and the severity of the EEG during wakefulness (p=0.02) and sleep (p=0.03). These results showed that less components are seen with worsening EEG activity (Table 3.17).

3.2.13. Obligatory ERP responses

In order to describe positive and negative deflections in the obligatory responses of infants with IS group mean average ERPs to frequent standard stimuli were computed. Two positive components labelled P150 and P350 were separated by the negative component N250. The obligatory components were replicable within and between subjects in both wakefulness and sleep (sect ref 2.7). Figures 3.31 and 3.32 and figures 3.33 and 3.34

are showing the replicability of the obligatory components P150, N250 and P350 during wakefulness and the P150 during sleep in 2 consecutive recordings at electrode F3 respectively.

Figures 3.35, 3.36 and 3.37 show mean group ERPs at the 1-4, 5-8, and 9-14 months in infants with IS compared to controls at electrode F3 in wakefulness and sleep respectively. The latencies of the P150, N250 and P350 appeared prolonged during sleep in the 5-8 and 9-14 months of infants with IS (Figures 3.36 and 3.37). The 1-4 months group appeared to have similar latencies compared to control group, but there was only one patient in the group of infantile spasms (Figure 3.35). The P150, N250 and P350 latencies of the 9-14 month group with IS appeared to be longer compared to the control group during wakefulness (Figure 3.37). On the contrary the latencies of the 1-4 and 5-8 months groups with IS appeared to have similar latencies to the control groups, but there were only 2 patients during wakefulness in the mean group averages of the infants with IS at 1-4 months (Figures 3.35 and 3.36).

The next figures are taken as examples to demonstrate individual infants with presence or absence of the obligatory components. Figure 3.38 shows an infant with infantile spasms aged 10 months during wakefulness with prolonged P150, N 250 and P350 components compared to the control group 9-14 months and figure 3.39 shows an infant aged 10 months with only a P150 component compared to the control group 9-14 months.

3.2.14. Novelty ERP responses

In order to describe positive and negative deflections in the novelty responses group mean average ERPs to novel stimuli were also computed. The novelty ERP components described in the control group during wakefulness (3.1.4.1) and sleep (3.1.4.2) were also detected in infants with infantile spasms. The novelty components were replicable within and between

subjects in both wakefulness and sleep. Figures 3.40 and 3.41 and figures 3.42 and 3.43 are showing the replicability of the novelty components N250 and P500 during 2 consecutive recordings at electrode M1 during wakefulness and sleep respectively.

The positive and negative components of the infants with IS had longer latencies compared to the control infants during wakefulness or sleep. Figures 3.44, 3.45 and 3.46 show group mean ERPs at 1-4, 5-8 and 9-14 months in infants with IS compared to controls during wakefulness and sleep at electrode M1 respectively. The latencies of the N250 and P500 of the IS group ERPs appeared to be prolonged compared to the control group in both states of awareness. Prolonged Nc1 and Nc2 latencies of group mean ERPs at 5-8 months in infants with IS compared to controls are shown at electrodes F3 and F4 in figure 3.47 during wakefulness.

There were not enough infants with IS to compute group mean averages of a similar age range and aetiology (Tables 3.11 and 3.12). The next figures have been selected to demonstrate that patients with unilateral abnormal hemisphere pathology have abnormal novelty ERPs in both hemispheres.

Figure 3.48 shows a 10 months old infant with a R middle cerebral territory infarct, which has been recorded only in sleep. The N250 and P500 latencies are prolonged at the mastoid (M1) and inferior temporal (P7) electrodes of the L hemisphere compared to the mean average of the 9-14 months control group. Despite normal N250 and P500 latencies on the R hemisphere, amplitudes of both components are reduced.

Figure 3.49 shows N250 and P500 latencies at electrode P8 (right hemisphere) and P7 (left hemisphere) in an 8 months old infant with a R cortical dysplasia in sleep, which are prolonged compared to averaged group ERPs for 5-8 months in control infants.

3.2.15. Latency differences between the IS and control ERP

As it was not possible to adequately transform the ERP data of the IS to normality, nonparametric ANCOVA calculations were carried out to compare the amplitudes and latencies with control subjects. The latencies of the P150, N2, P3 and Nc2 ($p<0.001$) and the Nc1 ($p<0.0001$) in infants with IS were still prolonged when compared to control subjects after adjustment for age during wakefulness (Table 3.18). During sleep the P150, P3 and the specific sleep component NCS ($p<0.001$) and the N250 ($p<0.008$) were also prolonged significantly after adjustment for age when compared to controls (Table 3.18).

3.2.16. Assessment of possible associations between ERP latencies and clinical factors

Using Spearman correlation coefficients no relationships between ERP latencies and clinical factors such as normal or abnormal development before seizure onset, normal or abnormal MRI brain results and EEG abnormalities such as presence of hypsarrythmia during sleep, moderate or severe EEG abnormality, persistent focal changes, exacerbation of EEG abnormalities by sleep, ictal recordings of infantile spasms met the criteria for significance having a p-value of less than 0.05.

CHAPTER 4: DISCUSSION OF RESULTS IN HEALTHY INFANTS

A critical part of this study was to obtain reliable and replicable ERP data in normal infants in order to assess the functional integrity and possible maturation of the temporal lobe and to allow comparison with infants with infantile spasms.

4.1. Obligatory ERP responses

4.1.1. ERP components

There is currently no published cross-sectional study comparing auditory ERP latencies in normally developing infants during wakefulness and stage II sleep. In this study, a small negative deflection (N250) was found between two positive deflections called P150 and P350. The P350 was followed by a further negative deflection labelled N450. These components were seen in both wakefulness and stage II sleep. Although the N250 and P350 components were already seen within the first 4 months of age their peaks became more clearly separable with increasing age. This ERP component structure is in agreement with previous studies (Section 1.2.3.1.1.2, Kushnerenko *et al.*, 2002a; Jing *et al.*, 2006). The topographical distribution of ERP components P150 and P350 showed a clear inversion of polarity across the superior temporal plane, best explained by a generator in the superior temporal gyrus.

4.1.2. Age dependence of ERP peak-latencies

In our study the latencies of the P150, N250 and P350 significantly decreased with increasing age independent of arousal. This is in agreement with the study by Jing *et al* (2006), but contrasts with the study by Kushnerenko *et al* (2001) where only the P150

latency was reported to decrease with increasing age. The decreasing latencies with age may be evidence of a continuing maturation process in the temporal lobe of normal infants.

4.1.3. Effect of sleep on obligatory components

The latencies of the P150, N250 and P350 also decreased with increasing age significantly during stage II sleep, but were significantly longer than those measured in wakefulness. This result clearly shows that auditory ERP latencies in infants are dependent on the state of arousal and therefore when analysing auditory ERPs it is particularly important to distinguish between different states (Section 1.2.4). There are no infant studies for comparison, but studies in adults have also shown an increase in the latency of the obligatory components during stage II sleep (Nielsen-Bohlman *et al.*, 1991; Atienza *et al.* 2001; Crowley *et al.*, 2004). The present data suggest that the cerebral generators for the P150, N250 and P350 components are already present within the first 4 months of extrauterine life and that ERP components are identifiable during both wakefulness and sleep.

A reason for the delayed latencies during sleep may be the fact that during stage II of non-rapid eye movement (NREM) sleep thalamocortical neurons are also globally inhibited by increased GABA (y-aminobutyric acid) input from the thalamic reticular nucleus, resulting in much lower firing rates compared to wakefulness. This inhibition is partly modulated by the cholinergic and aminergic neurotransmitter systems in the pontine reticular formation. During wakefulness the pontine aminergic system is tonically activated and inhibits the pontine cholinergic system. During NREM sleep the aminergic inhibition decreases and the cholinergic excitation waxes (Pace-Schott *et al.*, 2002). The longer latencies of the P150 N250 and P350 in stage II sleep may then be secondary to different levels of energy metabolism in cortical neurons. PET studies of NREM sleep have shown a decreased cortical and thalamic energy metabolism and blood flow compared to wakefulness and

rapid-eye movement (REM) sleep. The energy metabolism during sleep decreases progressively with greater depth of NREM sleep (Pace-Schott *et al.,* 2002).

4.1.4. Are the infantile ERP peaks analogous to any childhood or adulthood peaks?

In the absence of an extensive developmental study using serial recordings no definite answer can be given, but each component will be discussed separately.

4.1.4.1. The infantile P150 as a possible precursor of the adult P50

The ERP (P150-N250-N450 complex) in the first 12 months of life identified in this study and by Kushnerenko *et al* (2002) is similar to the complex P100-N250-N450 recognized in children (Paetau *et al.,* 1995; Ceponiene *et al.,* 1998; Ceponiene *et al.,* 2002a). A persisting peak of the P150 with decreasing latency during infancy (this study, Kushnerenko *et al.,* 2002) and further decreasing latency between infancy and 5-6 years suggests that the P150 is the precursor of the childhood P100. The P100 develops into the adult P50 (P1) response by further decreasing latency from 5 to 20 years (Ponton *et al.,* 2000).

4.1.4.2. The infant N250 as a correlate of the of the childhood N250

In this study the latency of the infantile N250 decreased significantly over the first 14 months of age and may therefore be regarded to be the correlate of the childhood N250. The N250 gradually matures into the adult N2 from 5 to 20 years of age (Ponton *et al.,* 2000). The latency of the N250 has been reported to shorten with age but mainly from 9 years to adulthood without shortening between 4 and 9 years of age. The N250 amplitude is reported to decrease steadily with age, but continues to have a similar scalp distribution until adulthood and therefore the childhood N250 is suggestive of corresponding to the adulthood N2 (Ceponiene *et al.,* 2002b).

4.1.4.3. The infantile P350

The adult P2 appears to mature early, at around 5 years of age, since latencies did not change between 5 and 20 years of age (Ponton *et al.,* 2000). Whether the infantile P350 corresponds to the adult P2 remains unclear in the absence of a detailed developmental study of this component.

4.2. Endogenous ERP responses

4.2.1. Mismatch-negativity

The MMN as a possible tool was assessed, but was only shown in the group mean average of the 5-8 months group. An anticipated adverse SNR in infants with IS and the fact that the MMN was not reliably detectable in individual control infants were the reasons why the MMN could not be used as a tool to assess the temporal lobe function in infants with IS.

4.2.2. Novelty ERP components

Previous developmental ERP studies have utilized different numbers of electrodes and recording montages and have not commented on possible generators (Table 1.1). There is therefore a paucity of information on developmental changes in ERP topography that could provide insight into the functional maturation of specific cortical regions. This study used 19 electrodes and also commented on possible generators and the distribution of the ERPs. Novel sounds elicited prominent fronto-central "P3a" like responses of positive polarity (P250), and large amplitude negative components over bilateral inferior temporal and mastoid electrodes (lN250). Double peaks of the "P3a", the early P3a (eP3a) and the late P3a (lP3a), which are clearly separable during childhood (Ceponiene *et al.,* 2004) and adulthood (Escera *et al.,* 1998) were seen only inconsistently at frontal and central electrodes and were therefore not measured in all infants. In individual infants, where the eP3a and lP3a were separable, the early P3a clearly inverted its polarity over the mastoid and inferior temporal electrodes. However the finding that the late P3a did not invert its polarity at any electrodes, is in agreement with the adult (Escera *et al.,* 1998) and childhood

literature (Gumenyuk *et al.,* 2001). The lack of consistency of these early and late components might be due to physiological maturation in infants up to one year of age. The fronto-central distribution of the P250, the double peaks and the significant larger amplitude compared to deviants are supporting evidence of the P250 being the precursor of the adult P3a. Following the positive "P3a" component, novel sounds elicited robust slow components (P500) bilaterally in inferior temporal leads. Further components are fronto-central negativities, previously termed Nc, lasting from 500 to 1400 ms after stimulus onset. So far the Nc component has only been shown in infants using visual ERP (Courchesne *et al.,* 1981). In this study two components were clearly separated in individual and group mean averages: a first Nc1 peak with a latency of 500-1000 ms, and a second Nc2 peak at 1000-1400 ms. Two Nc components have also been found in children between 9 and 13 years of age showing peak latencies between 400-750ms and 800-1100ms (Ceponiene *et al.,* 2004). The Nc1 and the Nc2 components had opposite polarity at the parietal electrodes.

The "P3a" (P250) and negative (N250) components over both hemispheres showed an inversion of their polarity between mastoid (inferior temporal) and central electrodes, compatible with a generator site within the posterior superior temporal plane. This inversion is also seen between the positive P500 and the central component (NcS) bilaterally at the same electrodes. The frontal "P3a" (P250) components showed an inversion of their polarity over the parietal electrodes suggesting that their generator is more anteriorly located to the superior temporal plane. The presence of a P3a generator in the superior temporal gyrus is supported by the study by Alho *et al* (1998), which identified a generator of the magneto-encephalographic P3 in the superior temporal plane in adults. These findings, indicating two or more generators within the superior temporal plane and a further generator within the frontal lobe, are consistent with a neural network consisting of several generators as suggested by intracranial recording studies in adults (Halgren *et al.,* 1995a; Halgren *et al.,* 1995b; Baudena *et al.,* 1995).

4.2.2.1. Effect of sleep on novelty processing

The P250, N250 and P500 were clearly seen during stage II sleep. These findings strongly support the concept of auditory novelty processing in sleep stage II in infancy and are consistent with findings in adults (Atienza *et al.,* 2001). The central P250 components and frontal P250 components showed also a polarity inversion with the N250 over the mastoid and parietal electrodes. Two frontal negative components labelled Nc1 and Nc2 over the frontal electrodes and a further central component, labelled NcS, (peaking 80ms earlier than the Nc1 and seen only over the central electrodes C3, C4 and Cz) seen in the present study may reflect further novelty processing during sleep stage II. The central NcS components showed a reversal of polarity with the P500 across inferior temporal leads (Section 3.1.4.2) while the frontal Nc1 and Nc2 showed a reversal of their polarities over the parietal electrodes P3 and P4 and Pz respectively. These findings are also consistent with a neural network consisting of multiple generators.

The distributions and latencies of the novelty components were similar in both wakefulness and sleep. The larger amplitudes of the novelty amplitudes during sleep compared with wakefulness have not been reported previously.

The identification of ERP components in the developing child is often problematic especially when comparing different states of arousal. If the components P500, Nc1 and Nc2 seen in sleep represent the same components seen in wakefulness, then the latencies show a dramatic reduction, which is both unexplained and unprecedented. If they represent different components, this argues that the auditory signals are processed completely differently in wakefulness and sleep in the developing brain, a phenomenon not seen in the mature brain. At this stage, there are no clear additional data to indicate which of these possibilities is likely to be correct.

4.2.2.2. Age related latency changes of novelty ERP components

The latency of the novelty P250 decreased with age during wakefulness, while the long latency component P500, Nc1 and Nc2 showed a more marked decrease in latency with age independent of arousal. These latency changes appear therefore to follow a normal maturational sequence.

4.2.2.3. Age related amplitude changes of novelty ERP components

The amplitudes of the N250-P250 demonstrated significant inverted-U-shaped age-dependencies during wakefulness, showing a maximum amplitude in the 5-8 months group. Similar results with maximum amplitude at 6 months using speech sounds have been shown by Vaughan and Kurtzberg (1992), but data from other studies using click or tone stimuli did not find this result (Barnet, 1975; Shucard *et al.,* 1987b; Shucard *et al.,* 1988). While 2 studies (Shucard *et al.,* 1987; Ohlrich and Barnet 1972) measured the amplitude from peak to peak, Vaughan *et al* (1992) measured the amplitude from baseline to peak. These different measurements may have contributed to this discrepancy. ERP peak amplitudes for visual evoked potentials also showed a maximum amplitude at 6 months of age (Vaughan *et al.,* 1992). As the synaptic density of the visual cortex reaches its maximum around 8 months (Huttenlocher *et al.,* 1982), followed by a decline it has been suggested that the inverted-U-shaped VEP amplitude parallels the time course of synaptic density (Vaughan *et al.,* 1992).

4.3. Infantile neural network for novelty

This study has provided the first evidence that the auditory detection mechanism for novelty is present in infants during wakefulness and sleep. This ability may already be present in newborns (Section 1.2.3.1.2.2). The findings of several generators are consistent with a neural network for novelty in infants (Section 4.2.2). Furthermore, our results have also shown that during stage 2 sleep interesting and surprising novel stimuli can be detected by the auditory system. As the ability to orient to novel events is critical for survival (Sokolov,

1963) one may even suggest that the auditory system continues preserving this "essential service" during sleep in order to maintain contact with the surrounding environment. This essential service may also protect from danger in the environment.

4.4. Hemisphere dependence of obligatory and novelty ERP latencies and amplitudes

The peak latency of the P150 was shorter over the right than the left hemisphere, irrespective of age and arousal. This is in contrast to the findings of Jing *et al* (2006) who detected a shorter P150 latency over the left compared to the right hemisphere. Shorter latencies over the right hemisphere were also seen for the novelty component Nc1 in this study. The peak latency of the P500 was also shorter over the right hemisphere but this effect was seen mainly during wakefulness. Although there is no direct corroboration of these findings, Chiron *et al* (1997) found a higher blood flow in the right hemisphere in children. The N250 was the only novelty component showing higher amplitudes over the left hemisphere. These disparate pieces of information open up the possibility that each hemisphere may have different patterns of maturation.

4.5. Neural mechanism possibly underlying the development of the obligatory and novelty ERPs in normal infants

The possible mechanisms underlying the maturation of infants ERPs may be divided into anatomical and physiological causes.

4.5.1. Anatomical causes

Postnatal cortical development during the first year of life is characterized by an increased synaptic density, i.e. the number of synapses per neuron, dendritic growth and an expansion in the total volume of cerebral cortex (Huttenlocher, 1979). There is an increased synaptic density in several brain regions including the auditory cortex, frontal cortex and visual cortex reaching a plateau around 3-9 months (Huttenlocher *et al.,* 1987; Huttenlocher *et al.,* 1997). The mean synaptic density is maximal at 3 months in the primary human auditory

cortex (Heschl's gyrus), at 8 months in the visual cortex and in the association areas of the frontal cortex only by two years of age (Huttenlocher, 1990; Huttenlocher *et al.,* 1997). Despite the early maximal synaptic density of the auditory cortex the anatomical maturation of the human auditory cortex is protracted and may be separated into three stages. During the first stage between the 3rd trimester and the 4th postnatal month mature axons are only present in the marginal layer, also called layer I, as seen by the pattern of axonal neurofilament expression. All other layers have no mature axons until the age of 5 months (Moore *et al.,* 2001). Although infants can precisely distinguish speech sounds, there is no anatomical route for transmission as the auditory cortex has only mature axons in the marginal layer (Moore, 2002). On the contrary the results of this study are showing clearly ERPs generated in the cortex. During the second stage between 6 months to 5 years the axons in the deep cortical layers continue to mature and increase in density, but the superficial layers have not yet started to mature. These deep-layer axons are identified as thalamocortical afferents indicating that auditory connections from the brainstem and thalamus are emerging auditory pathways between 5 months and a year. This may be supported by the fact that at 6 months of age infants begin to discriminate between prototype and variant versions of native and non-native speech sounds (Moore, 2002). The maximum amplitude of the novelty ERPs at 5-8 months group during wakefulness in this study and in the study by Kurtzberg using speech sounds may be further evidence for this maturation (Section 4.2.2.3).

The third stage of anatomical maturation, which is not complete before 12 years of age or later, includes the axons in the superficial layers. These fibres represent corticocortical connections, such as commissural axons connecting both cerebral hemispheres and association fibres connecting the auditory cortex with the temporal, parietal and prefrontal cortical lobes. This late maturation is reflected in frequency resolution reaching adult levels by the age of six years, but temporal resolution is still developing beyond the age of 12 years (Illing, 2004).

4.5.2. Physiological causes

Both synaptic density and the efficacy of the synapse change during development. Changes in synaptic efficacy during development occur both at the presynaptic terminal and at the postsynaptic site. The amount of transmitter available for release increases, and in addition transmitter quanta are released more synchronously, resulting in a faster rise of the postsynaptic potentials at the maturing synapse (Naka, 1964). Consequently this will result in decreased latencies to the initiation of an action potential (Eggermont 1988). Increasing myelination is a further factor contributing to the decrease in latency (Moskowitz *et al.*, 1983; Eggermont, 1988). An increased consistency of the brain response with age (Thomas and Crow 1994) resulting in a decrease of the trial-to-trial variability may also contribute to the shortening of the ERP peak latencies. One of the major neurotransmitter in the brain is γ-amino butyric acid (GABA), which has excitatory properties in early life before switching to its predominant inhibitory functions. Currently it is not known when this switch, related to the post-natal maturation of the chloride transporter gene KCC2, takes place in the human brain (Ben Ari, 2002; Ben Ari *et al.* 2005).

For the reasons mentioned above the neural maturation process of ERPs is therefore very complex, but may give some explanations why ERP latencies seem to decrease more evenly over age in contrast to the non-linear changes of ERP amplitudes.

4.6. Conclusions

The obligatory and endogenous components (novelty) of the ERPs were detected reliable and replicable in the control infants. There was a clear age dependence of all obligatory components independent of arousal. The novelty components also showed an age and sleep dependency. It was therefore reasonable to compare these results with those in infants with IS.

CHAPTER 5: DISCUSSION OF ERP FINDINGS IN INFANTS WITH INFANTILE SPASMS

The processing of auditory stimuli in the temporal lobe was investigated using auditory ERPs (Section 1.2.2), in order to test the hypothesis that the temporal lobe is functionally abnormal in children with infantile spasms. One of the primary aims of this study was therefore to compare the ERPs in infants with infantile spasms with the findings in the normally developing infants. In addition we investigated whether initial ERPs were predictive of the neurodevelopmental outcome at 2 years of age (Section 1.3.1.4). Variables documented here were age at seizure onset, response to treatment (seizure control after 2 weeks), development before the onset of spasms, and MRI findings in order to determine whether these findings were also related to initial ERP at presentation and developmental outcome at 2 years. As the ERP recordings of control infants showed clear differences between wakefulness and sleep stage 2, we carried out these investigations in both wakefulness and sleep (Sections 4.1.3 and 4.2.2.1). One of the major anticipated problems in the analysis of the ERP data of the infants with IS was an abnormal EEG with an abnormally low SNR. Before discussing and interpreting the ERP findings in infants with IS in the context of the SNR, the literature on the possible effects of epilepsy, cortical malformations, AEDs, and developmental delay on auditory ERPs in infants and children will be reviewed.

5.1. Influence of epilepsy, malformations, AEDs and developmental delay on auditory ERPs

Epileptogenesis, organic brain damage, underlying developmental delay, AED therapy and clinical seizures are likely to be interrelated and may influence auditory event related potentials in patients with epilepsy. There are no studies in infants and only a few studies in children with epilepsy reporting auditory ERP findings. The P300, also called P3b, which is

elicited only by active participation of the subject, has been studied most extensively (Section 1.2.3.1.2.2).

5.1.1. Influence of epilepsy and cortical malformations

A recent study of 45 patients with generalised seizures, 55 patients with partial seizures and 20 patients with intractable seizures showed significantly longer P300 latencies in the intractable and partial groups when compared to 25 control subjects (Celebisoy *et al.*, 2005). While patients with partial or generalised seizures were taking only one antiepileptic drug, patients with intractable seizures were using several combinations of AEDS, which may have confounded the result of the prolonged latency in the intractable group. The influence of AEDs on the P300 latency was not studied or commented on in this study. The duration of epilepsy, seizure frequency and the cerebral imaging pathologies were also not significantly correlated with the delayed P300 latencies.

Visual and auditory event related potentials were recorded in 32 children with epilepsy with abnormal MRI brain scans and 18 children with normal MRI brain scans and compared to data of 21 normally developing children (Turkdogan *et al.*, 2003). The mean latencies of the N2 (Section 1.2.3.1.1.1) and the P300 components of visual event related potentials and auditory event related potentials were significantly longer in all children with epilepsy compared to controls, but there was no significant difference in latency between children with epilepsy having normal or abnormal MRI head scans. The prolonged latencies were also not significantly related to the number of AEDs (mono-versus polytherapy). The small number of patients having generalised seizures did not allow comparison with the group having partial seizures.

Abnormal P300 latencies have also been shown in children with symptomatic partial, idiopathic generalised and idiopathic partial epilepsies (Konishi *et al.*, 1995). The prolongation was greatest in the patients with symptomatic partial epilepsies. The latter group also had the largest number of children with mental retardation treated with 2

antiepileptic drugs, which may have contributed to the prolonged P300 latency in the group with symptomatic partial epilepsy. The shortening of the P3 latency with age was small in all three groups and different in each epilepsy syndrome compared to controls.

In summary most of these studies reported prolonged P300 latencies in patients with epilepsy compared to controls. Patients with partial epilepsy had longer P300 latencies compared to patients with idiopathic epilepsy. Although there are no published auditory event-related potential studies in patients with cerebral malformations without seizure activity, an abnormal MRI of the brain in children with epilepsy was not more significantly correlated with a prolonged P300 latency then a normal MRI in children with epilepsy (Turkdogan *et al,*. 2003; Celebisoy *et al.,* 2005).

5.1.2. Influence of AEDs

In the current study all 28 infants, including 14 infants on a combination of at least 2 drugs, were treated with AEDs (Section 3.2.3). Only 6 patients had no seizures within 2 weeks of beginning of treatment. This poor response is most likely due to treatment of patients with IS at a tertiary referral centre. The literature on AEDs affecting ERPs is contro-versial. Shorter P300 latencies were found in a heterogenous group of patients with epilepsy having monotherapy compared to those receiving polytherapy (Triantafyllou *et al.,* 1992). Patients with temporal lobe epilepsy showed no differences in P300 latencies between monotherapy compared to polytherapy (Fukai *et al.,* 1990). A prolongation of the P300 latency was recorded in children with epilepsy undergoing monotherapy with supratherapeutic serum levels of carbamazepine or phenytoin (Enoki *et al.,* 1996). One study including seventy-three children (age 7-15 years) with newly diagnosed epilepsy including partial and generalised seizures compared the auditory P300 before and 6 and 12 months after antiepileptic drug therapy with either carbamazepine, phenobarbital or carbamazepine (Chen *et al.,* 1996). The P300 latencies were increased in children receiving phenobarbitone but not in children receiving carbamazepine and valproate. The P300 latencies of these epileptic children before treatment were not compared to children not having epilepsy.

Several studies exploring the effects of ACTH and corticotropin-releasing hormone on late auditory evoked potentials in adults have shown inconclusive results concerning amplitude/latency of the N1 and P2 amplitude (Hartmann *et al.*, 1996). The P300 latency did not change after a single dose and prolonged intranasal administration of ACTH (Smolnik *et al.*, 2000).

In summary there is little evidence that AEDs have a major effect on auditory processing and therefore delayed ERP latencies unless the medications were used in supratherapeutic doses.

5.1.3. Influence of developmental delay on ERPs

Are auditory ERP latencies also prolonged in patients with developmental delay (DD) or mental retardation (MR) not having epilepsy? The Down's syndrome (DS) has been most often studied as an example of developmental delay. There are only two infant studies using click evoked ERP responses comparing sleeping normal infants with sleeping infants with DS (0-3,3-9 and 9-14 months) not having seizures (Barnet *et al.*, 1967; Barnet *et al.*, 1971). The so-called "N2-P2-N3" was recorded at the electrode Cz during sleep, but the sleep stage was not recorded. Significantly greater amplitudes of the P2-N3 component but no latency changes were recorded in DS compared to normal control groups (Barnet *et al.*, 1967). A further study using auditory clicks also showed no latency changes between normal control and infants with DS (Barnet *et al.*, 1971). The different nomenclature and montage makes a direct comparison with this study and other studies difficult (Section 1.2.3.1.1.2). A further study comparing normal developing infants with infants having Down syndrome using several electrode placements according to the 10-20 systems might be useful to confirm these findings. However long latency auditory event related potentials recorded in 12 subjects with Down syndrome aged between 11 and 19 years showed prolonged latencies of all components from N1 to P3 compared to normal controls of similar age (Diaz *et al.*, 1995). Lincoln *et al* (1986) had shown similar results comparing

Down syndrome children with normal children. Adults with Fragile X syndrome, the most common form of inherited mental retardation, also showed prolonged P3 latencies (St Clair *et al.*, 1987) and children with Fragile X showed no habituation of the N1 and an absence of N2 sensitisation for repeated tones in an auditory oddball paradigm (Castren *et al.*, 2003). By contrast with studies in Down syndrome, mental retardation and Fragile X syndrome, the most consistent P300 abnormality in autistic patients is amplitude attenuation while the latency remains unaffected (Bomba *et al.*, 2004).

In conclusion there may be some evidence that a developmental delay in infants without seizures is not associated with prolonged ERP latencies. On the contrary in childhood and adulthood there are several auditory ERP studies showing clearly the association between prolonged ERP latencies and developmental delay.

5.2. Auditory ERPs of infants with IS and the issue of SNR

Having presented the literature background of epilepsy, AEDS, cortical malformations and developmental delay as possible causes for auditory ERP latency changes, the findings of the infants with IS in our study will be discussed now. There was no correlation between any ERP components and development at presentation, EEG abnormalities or underlying MRI aetiology. There are currently no studies in the literature correlating auditory ERPs with cognitive development during childhood. Auditory ERPs may generally not have a correlation with cognitive development or the developmental assessment was not sensitive and fine graded enough to show a correlation Future studies are certainly required to correlate cognitive outcome with ERPs. There were significant latency differences between the group of infants with IS and the group of normally developing infants during wakefulness and sleep. The discussion of the results will be separated according to obligatory and endogenous components.

5.2.1. Obligatory components

The latency of the P150, which is the first positive component of the exogenous components was significantly longer during both wakefulness and sleep in infants with IS compared to control infants. As the P150 is the possible precursor of the adult P50 (Section 4.1.4.1), it is suggested that the abnormal latencies of the P150 in infants with IS are compatible with an auditory processing deficit in the primary auditory cortex. All three obligatory components were only present in 34% of infants with IS during wakefulness and in 23% during sleep respectively. With a severe EEG abnormality fewer components were present during wakefulness and sleep. After adjusting for the SNR using logistic regression controls were still 5 times more likely to have all components identified during wakefulness. However, during sleep there was no difference between patients and controls in terms of the proportions with all components identified.

5.2.2. Endogenous components

The latencies of the N250 and the P500, which are suggested to be generated in the posterior superior temporal plane (Section 4.2.2) were also significantly delayed in patients with IS during both wakefulness and sleep compared to controls. Although this evidence points to major processing deficits in the temporal lobe, both the frontal Nc1 and Nc2 components were significantly delayed during wakefulness in IS. The latency of the sleep component NcS was also significantly delayed compared to controls. All endogenous components were present in only 42 % of patients with IS during wakefulness and 61% during sleep. With a severe EEG abnormality fewer novelty components were identifiable during wakefulness and sleep. After adjusting for the effect of SNR using logistic regression control subjects were 4.4 times more likely to have all novel components detected than patients with IS ($p=0.08$) during wakefulness. During sleep controls were 9.6 times more likely to have all components detected than patients with infantile spasms ($p=0.07$). This is weak indication that the differences in the detection of components are independent of the SNR during wakefulness.

These data provide therefore the first indication that the absence or prolonged latencies of the obligatory or endogenous components may not be due to an abnormal SNR but may be related to abnormal auditory processing in infants with infantile spasms.

5.3. Abnormal auditory processing in the syndrome of IS

There are no other reported studies having recorded auditory event related potentials in infants with epilepsy, but the prolonged obligatory and endogenous latencies in both sleep and awake state of IS are compatible with compromised auditory processing. This study has shown that auditory processing is already compromised at the lowest cortical level, the primary auditory cortex, in infants with infantile spasms. This is supported by the abnormal P150 component, which is likely to be generated in the primary auditory cortex (Section 4.1.4.1). The temporal lobe is part of the network processing auditory novelty stimuli (Section 1.2.3.1.2.2). The latencies of the endogenous components were abnormal over the frontal and temporal electrodes. The fronto-temporal system is essential for directing attention to novel auditory events in order to develop normal interaction with the environment. The absence or delayed latencies of the novelty components may therefore be the neurophysiological expression of a compromised auditory novelty detection mechanism of speech and environmental stimuli and the indifference to their surrounding. The abnormal ERP latencies during sleep reinforce the evidence of continued interruption of auditory processing.

It is not known whether antecedent auditory processing in the thalamus, midbrain and brainstem was also affected in our patient population. Abnormal processing in these parts of the auditory pathway could have had downstream effects on cortical auditory processing in the temporal lobe. Brainstem auditory evoked potentials (BAEPs) have been reported to be abnormal in up to 50% of patients with IS (Kaga *et al.*, 1982; Curatolo *et al.*, 1989; Miyazaki *et al.*, 1993).

These findings therefore support the main hypothesis of a dysfunctional temporal lobe in the syndrome of infantile spasms, but cannot exclude a dysfunction at an earlier auditory processing stage.

There can be no definite answer whether the infantile spasms caused the delayed ERP latencies due of the lack of antecedent comparable studies. There is some evidence that infants with Down syndrome with developmental delay, but without seizures have not shown delayed latencies. As the prolonged latencies in this study are also not simply due to an abnormal SNR, it is likely that the IS are a necessary factor compromising auditory processing in infants with IS. In order to further support this hypothesis, it would, however, be essential to record infants with a high risk of developing IS both before and after the onset of spasms. Infants with TS, in which IS are common would be an ideal group to study. A study recording auditory event-related potentials in infants having other epilepsy syndromes then IS will further help to determine if the delayed latencies are specific for the syndrome of infantile spasms.

The possible effect of AEDs on auditory ERPs in infants with IS especially are unknown as there can't be studies comparing infants having epilepsy on AEDs with normal controls on AEDs. Nevertheless it may be possible to record ERPs in infants with IS before treatment with AEDs. Only supratherapeutic doses or polytherapy with AEDs seem to have affected auditory processing in children with epilepsy.

There was also no correlation between an underling MRI abnormality and auditory ERPs in this study, but the latencies or amplitudes were prolonged on both hemispheres in the individual patients with an underlying cortical dysplasia or middle cerebral territory infarct (Section 3.2.15). Therefore it is likely that the infantile spasms may have contributed to the prolonged latencies or reduced amplitudes on the hemisphere without MRI abnormality.

5.4. IS in the context of an immature auditory cortex

The findings of delayed auditory processing in the primary and secondary auditory cortex have to be interpreted in the context of a very immature auditory cortex during the first year of life (Moore *et al.,* 2001; Moore, 2002). In normal developing infants axons radiate into the deeper layers 4, 5 and 6 of the auditory cortex only between 4 to 5 months and 1 year of age respectively. The process of maturation of the auditory cortex is possibly compromised by infantile spasms occurring between 4-8 months of age altering the dentritic and synaptic organization of the auditory cortex. Some evidence supporting damage of the auditory cortex by seizure activity is shown by electrical kindling changing the interictal temporal response properties of single units recorded from the primary auditory cortex in cats (Valentine *et al.,* 2005).

5.5. Summary and conclusions

This is the first study showing that auditory obligatory and novelty ERPs are delayed in infants with IS during both wakefulness and sleep compared to normal controls. Abnormal auditory processing in the primary auditory cortex and also abnormal auditory detection support the general hypothesis that there is an abnormality of the development of the auditory neural network in the temporal lobe in infants with IS.

As the auditory cortex is very immature during the first years of life it is suggested that infantile spasms may interfere with crucial maturational processes during this time period. This may involve interference with synaptogenesis, pruning of synapses, dentritic spine development and possible changes in neurotransmitter systems. There is also evidence from the Landau Kleffner Syndrome, a later onset epileptic encephalopathy that the continuous discharges are associated with atrophic superior temporal areas (Takeoka *et al.,* 2004). If infantile spasms are causing the delayed auditory processing one might therefore tentatively speculate that the temporal cortices in infants with IS may also show acutely atrophic changes, but may also appear normal due a normal number of synaptic connections which

may not have not been incorporated into functioning units. A possible outcome may be therefore be a "rewired temporal lobe" which may then have forward-feeding effects onto the processing by further networks outside the temporal lobe with the consequences of abnormal cognition seen in infants with infantile spasms. Infantile spasms may result from a particular temporal desynchronization of several central nervous system developmental processes, resulting in an encephalopathy with specific seizures and a characteristic EEG (Frost and Hrachovy 2005)

Our model emphasises the vulnerability of the immature temporal lobe to infantile spasms during development in the first year of life

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CHAPTER 6: FIGURES

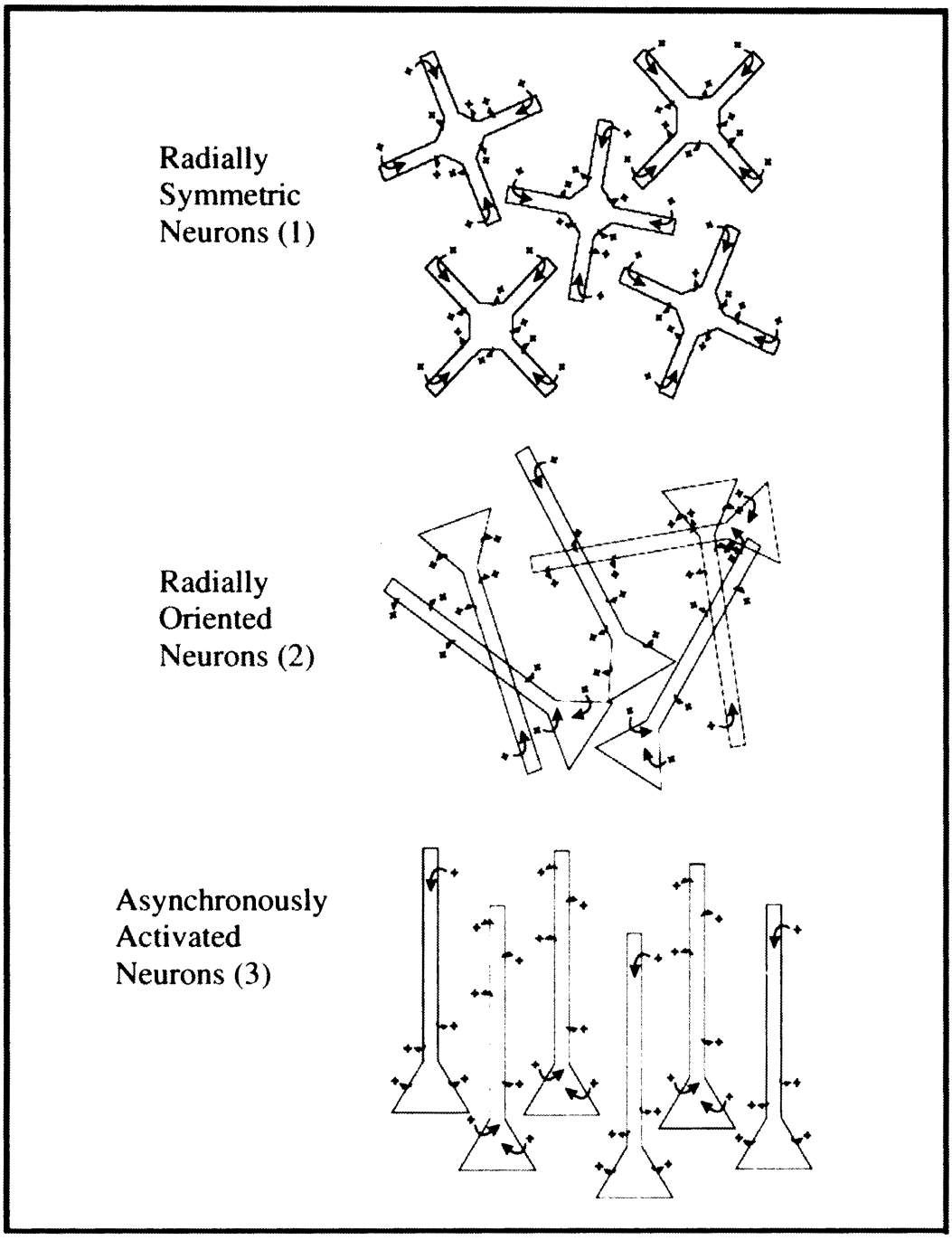


Figure 1.6. Neurons, which are radially symmetric (1), randomly oriented (2) or asynchronously activated (3) do not produce externally observable electric or magnetic fields (Rugg 1996).

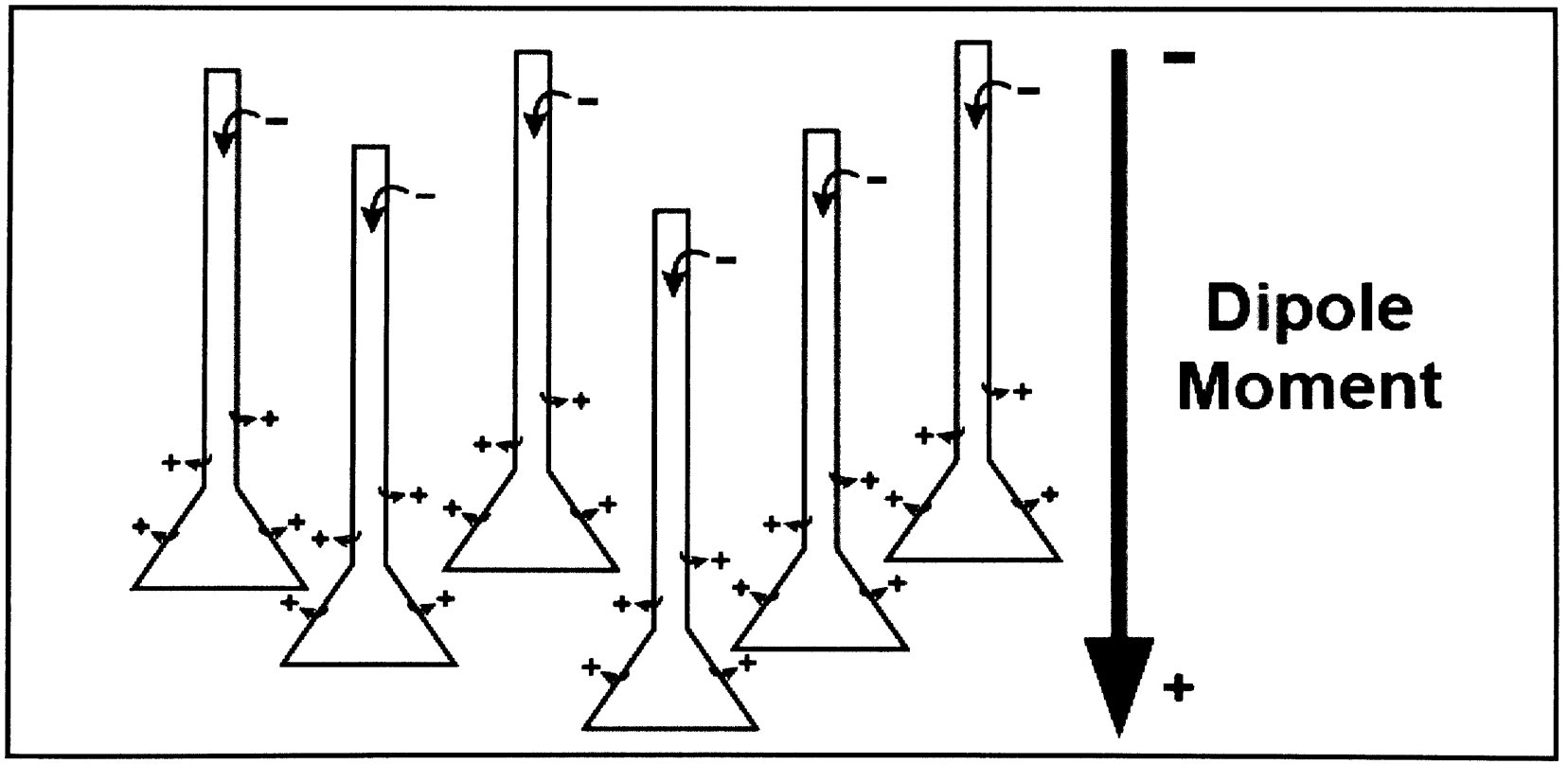


Figure 1.7. Open field source configuration. Neurons which are non-radially symmetric, spatially aligned and synchronously activated add up to produce externally observable electric and /or magnetic fields (Rugg 1996).

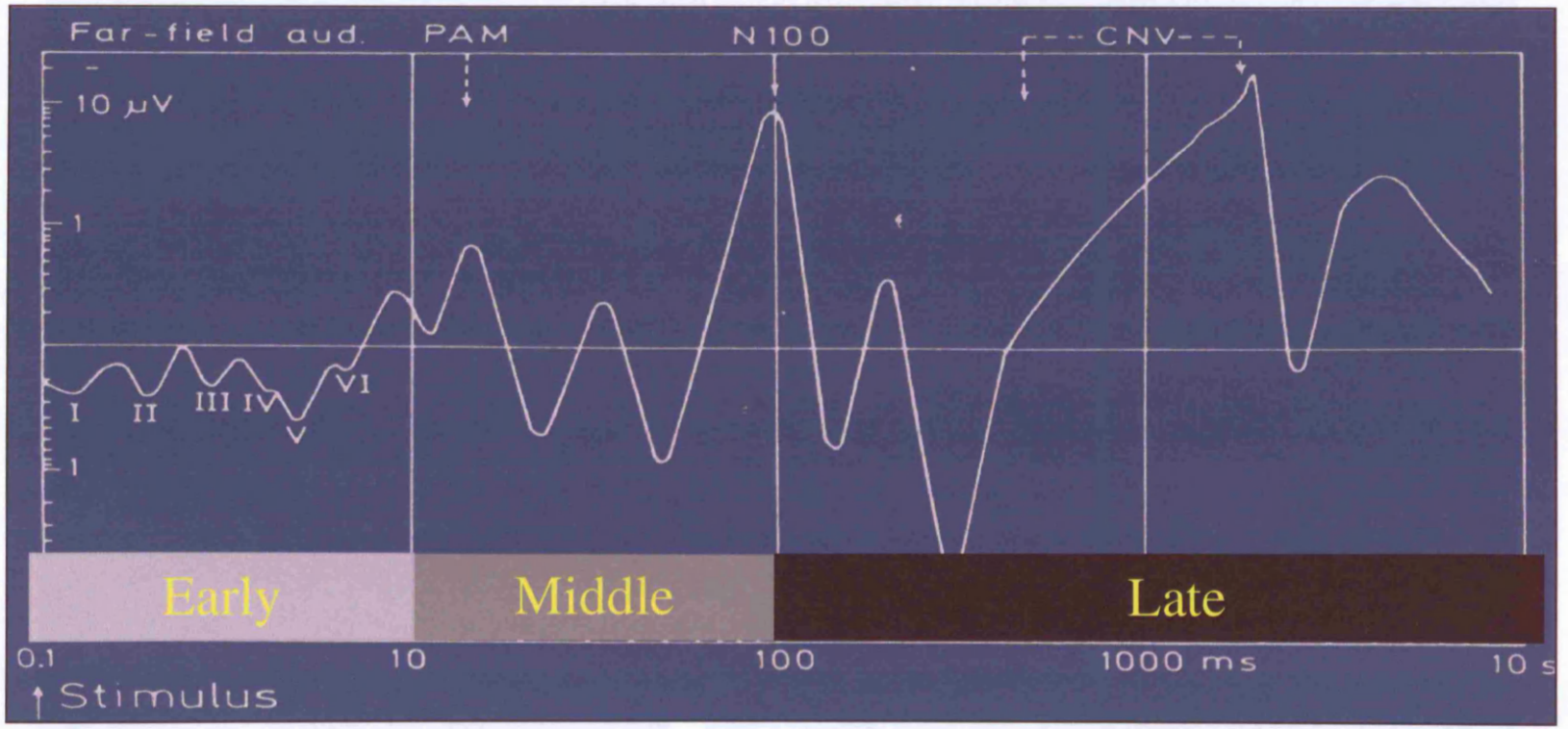


Figure 1.8. Schematic representation of potentials evoked following auditory stimulation. Both amplitude (µV) and latency (ms) are displayed using logarithmic scales. Potentials are grouped into three categories: early, middle and late (Cooper et al., 1980).

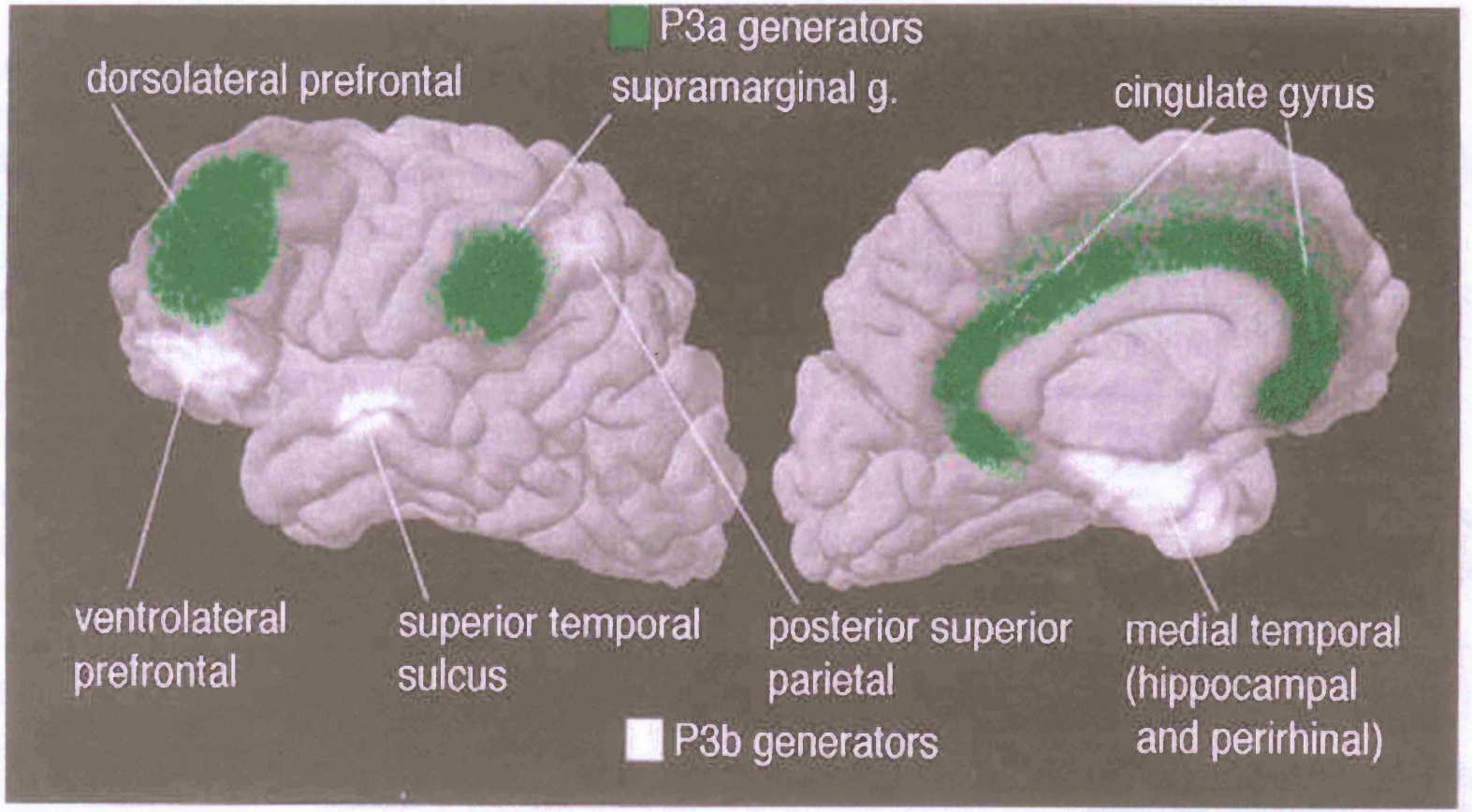
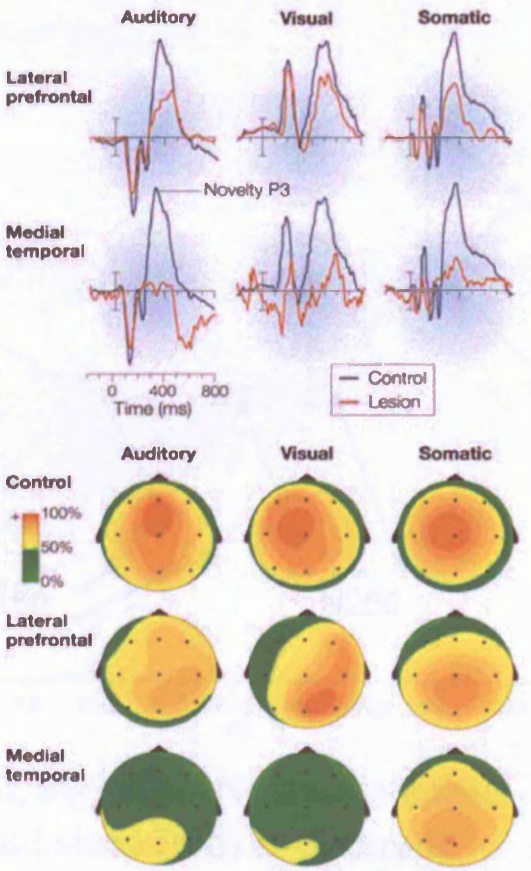


Figure 1.9. Summary of the brain areas where P3a and P3b were found to be generated (Halgren et al., 1998).

Figure 1.10. Upper part shows plots of the novelty P3 elicited in the auditory, visual and somatosensory modalities in patients with lateral prefrontal or posterior medial temporal lesions (red lines) and matched control groups (blue lines). Positive is plotted upwards, Scale bar for the auditory and somatosensory plots Scale bar for the visual plots, Lower part shows topographic maps illustrating the scalp topography of the novelty P3 in two patient groups and the control group. The novelty P3 had a frontal topography in control subjects across all modalities whereas the novelty P3 topography was more posterior in patients with prefrontal lesions, and was virtually eliminated in patients with medial temporal lesions (Ranganath et al., 2003).



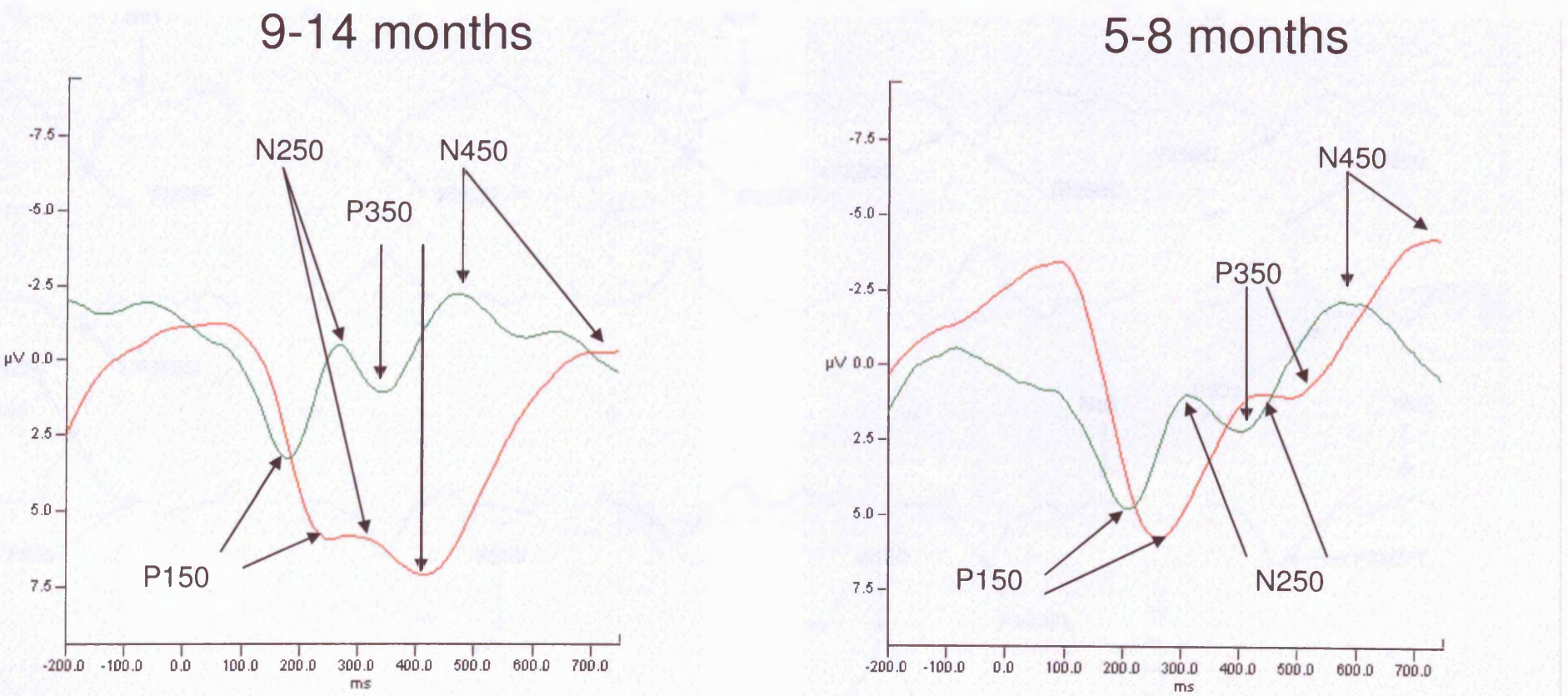


Figure 2.1. Group mean ERPs of the components P150, N250, P350 and N450 in controls at 5-8 months and 9-14 months during wakefulness (green) and sleep (red) at electrode F3.

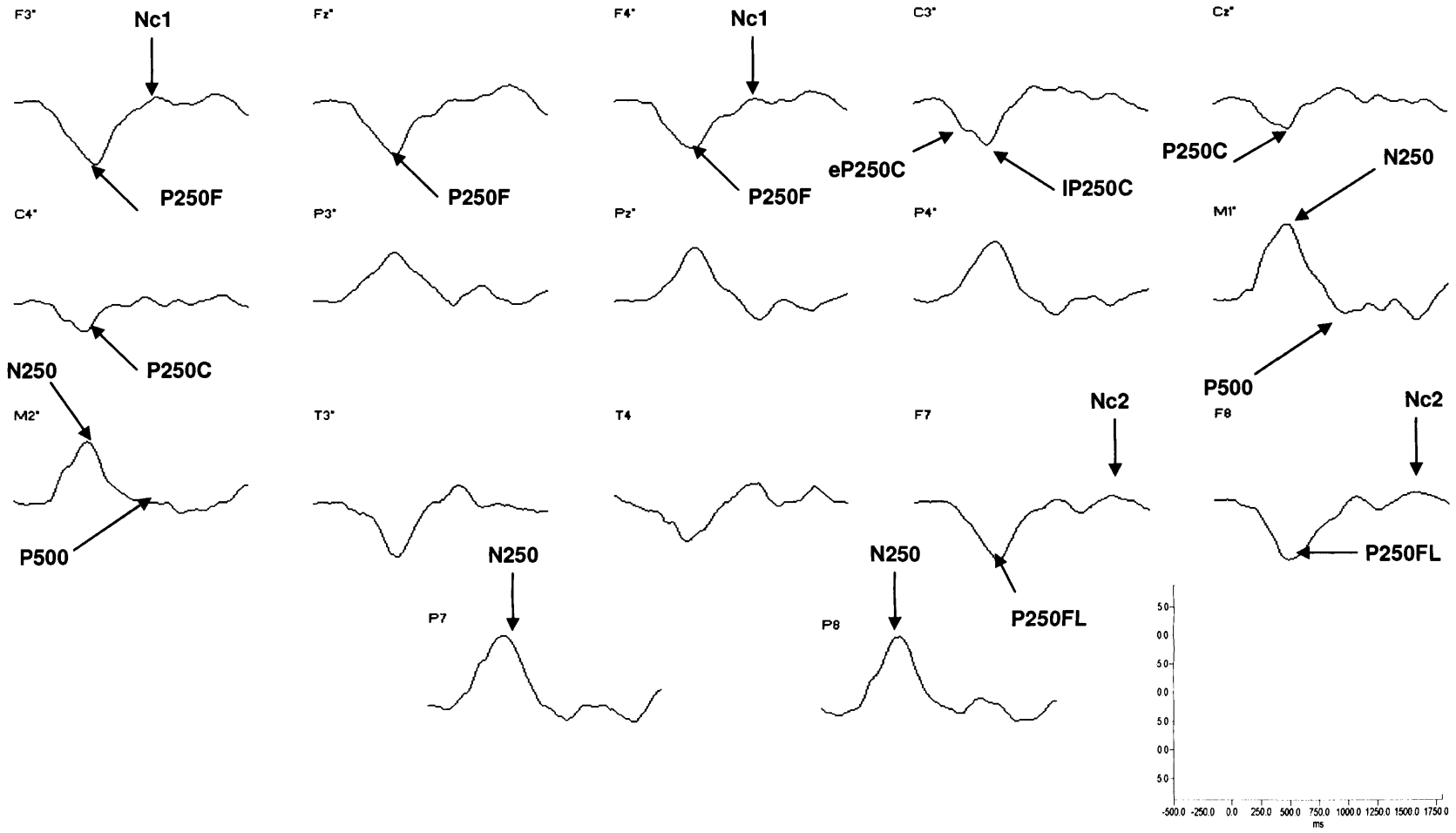


Figure 2.2. Group mean ERPs to novel sounds at 5-8 months during wakefulness.

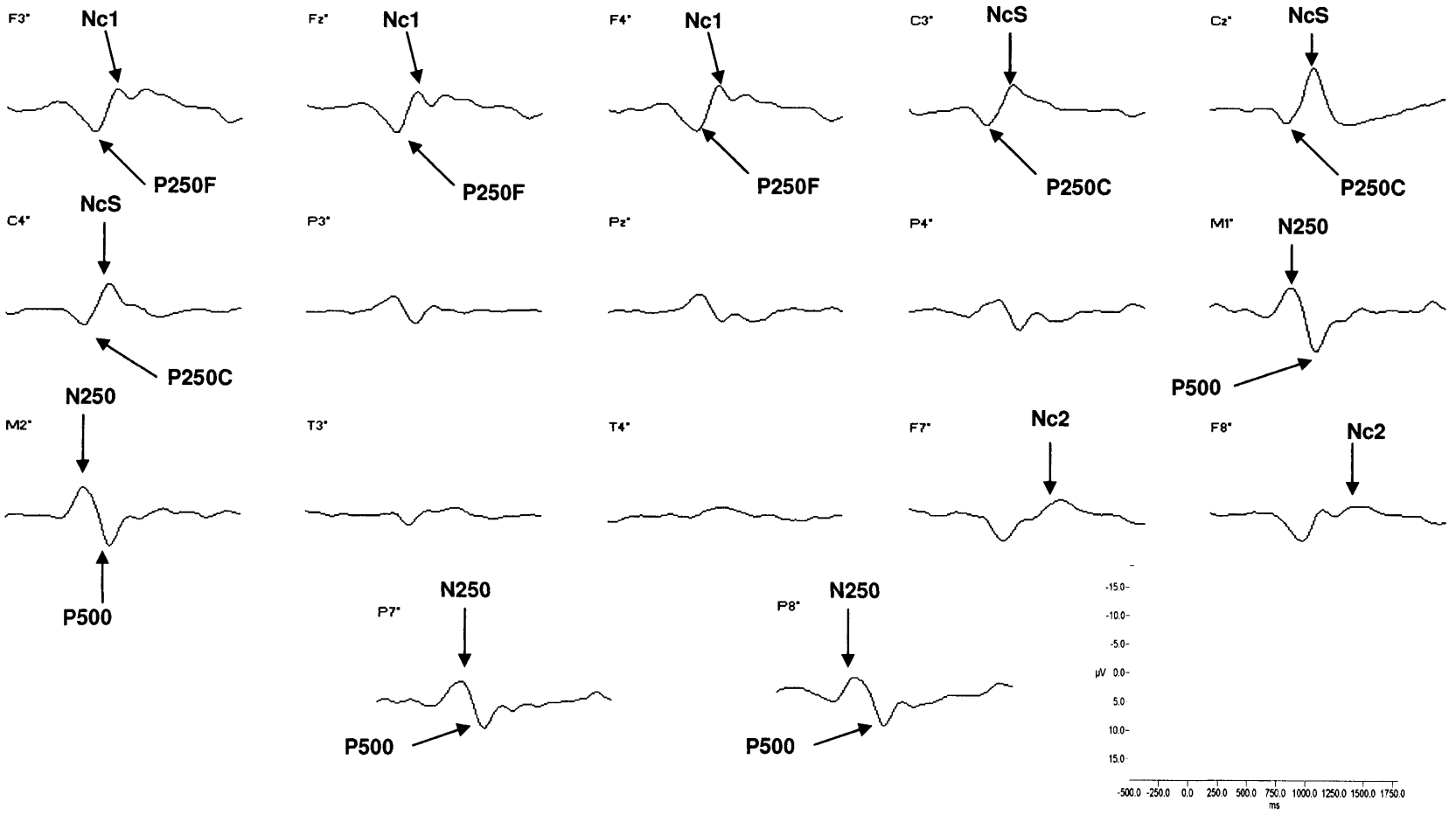


Figure 2.3. Group mean ERPs to novel sounds at 5-8 months during stage sleep II.

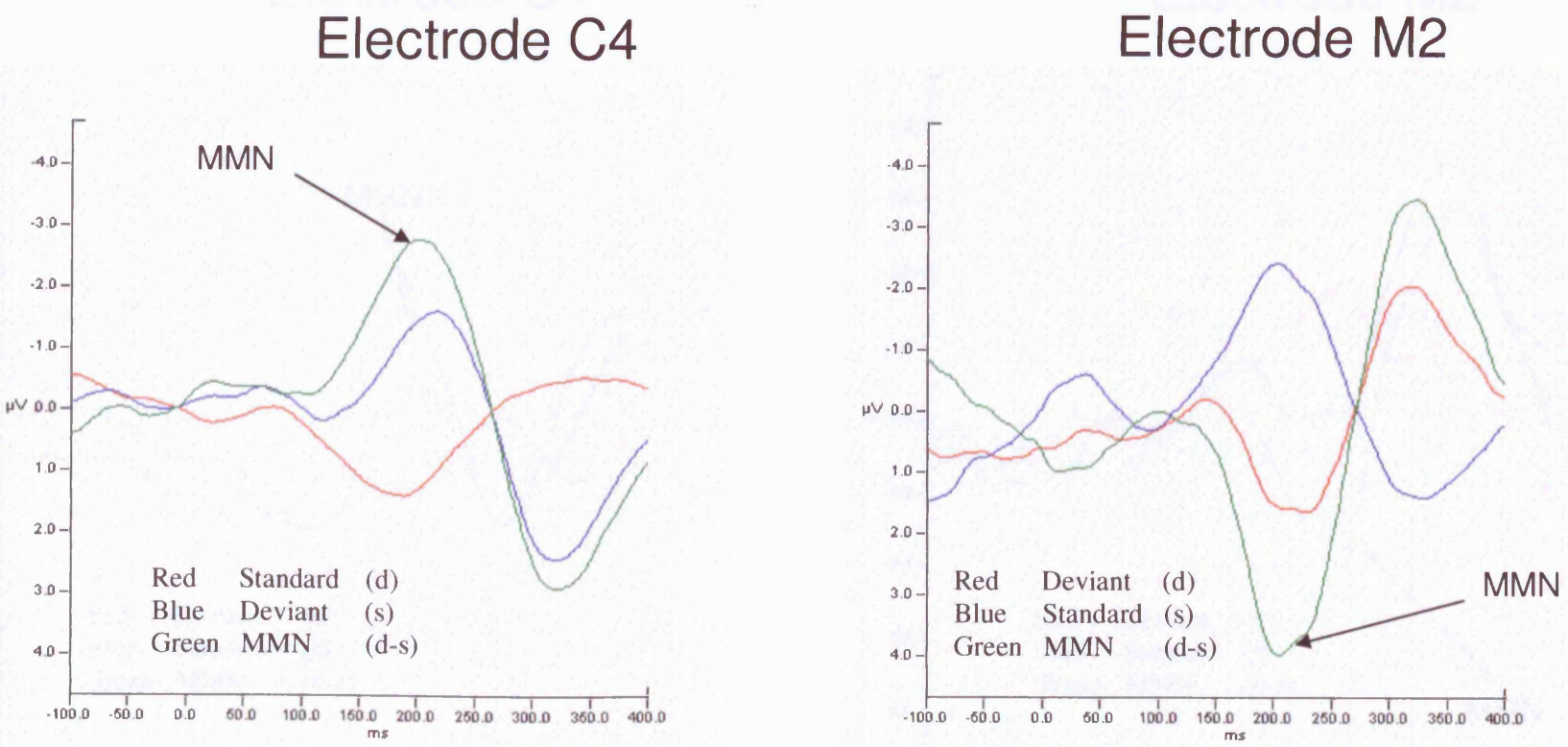


Figure 3.1. Group mean ERPs of the control group at 5-8 months show a MMN during wakefulness at electrodes C4 and M2.

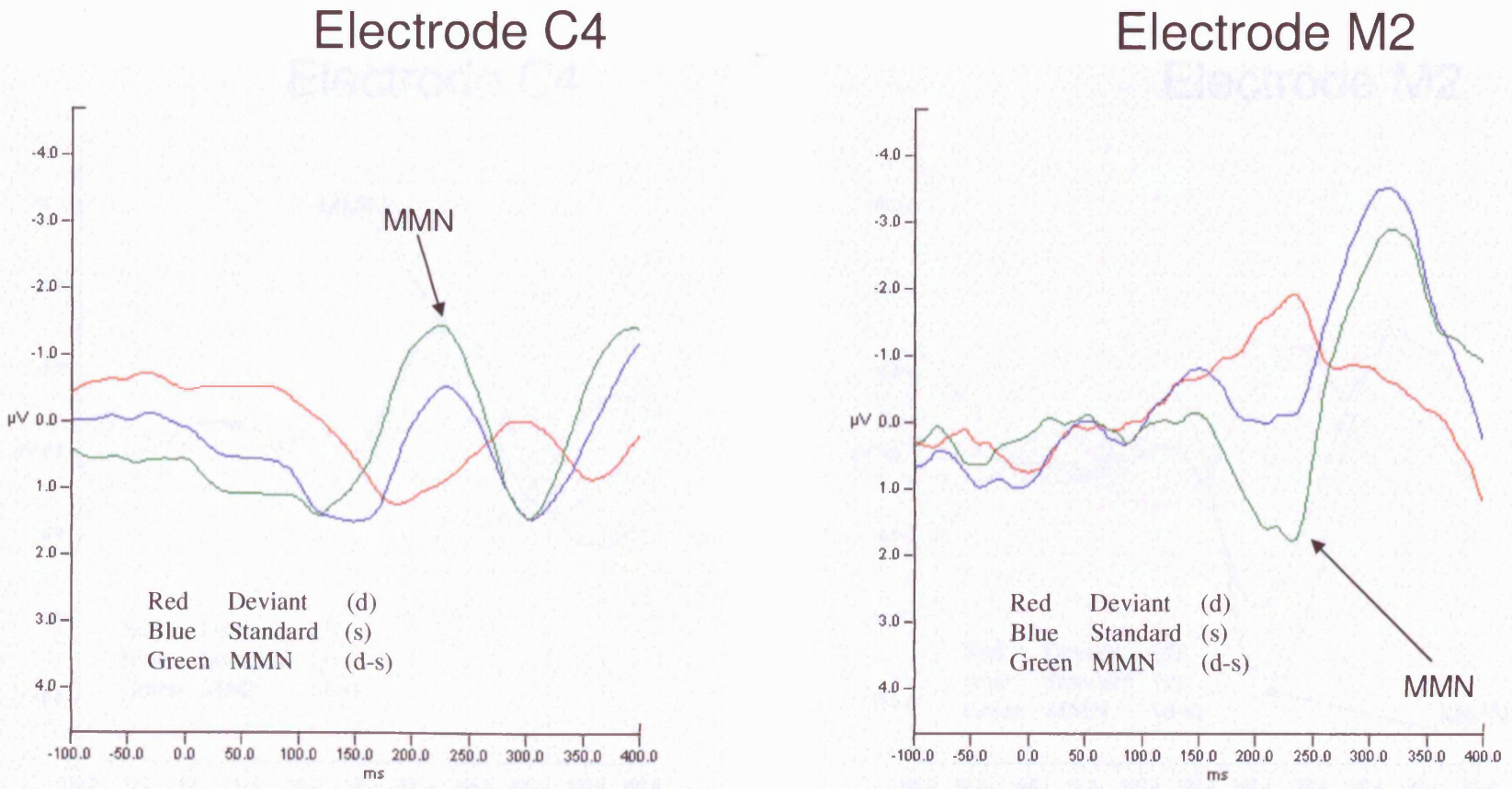


Figure 3.2. ERP of a control infant at 6 months shows a MMN during wakefulness at electrodes C4 and M2.

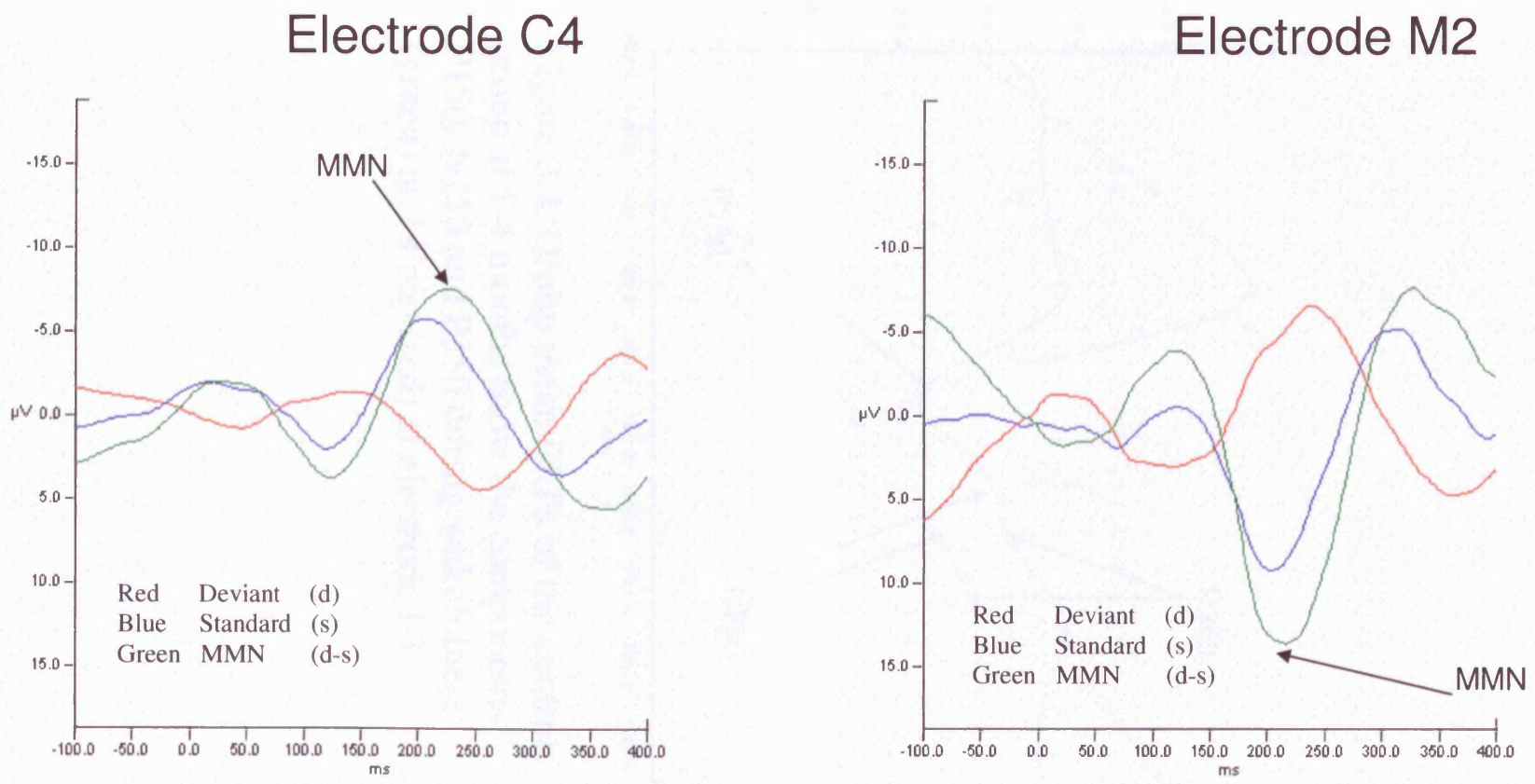


Figure 3.3. ERP of a control infant at 7 months shows a MMN during wakefulness at electrodes C4 and M2.

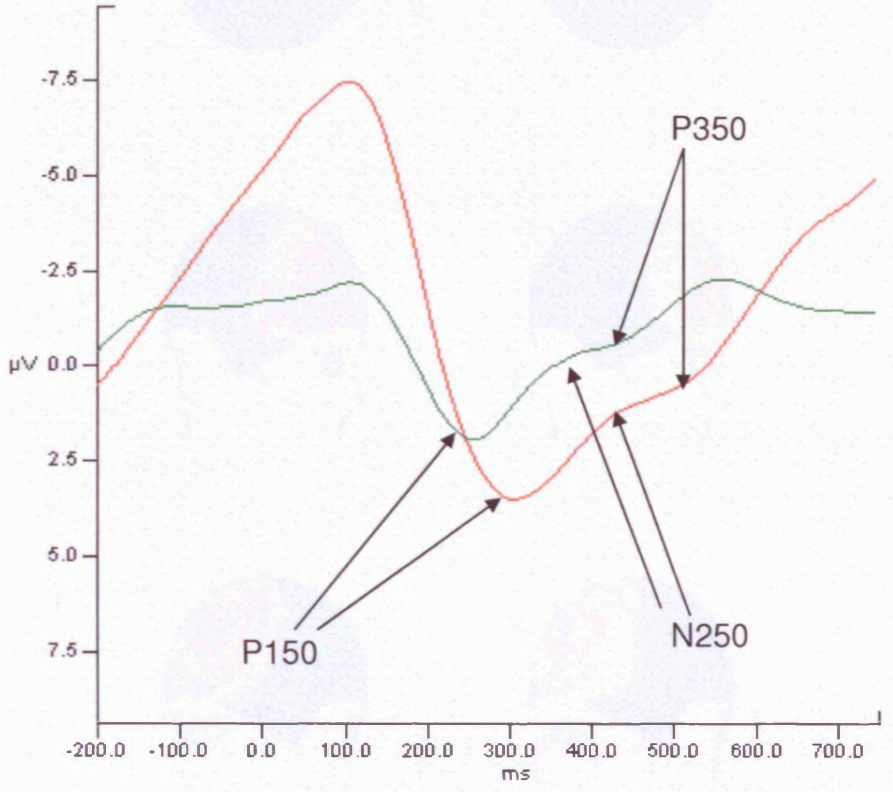


Figure 3.4. Group mean ERPs of the control group at 1-4 months show the components P150, N250 and P350 during wakefulness (green) and sleep (red) at electrode F3.

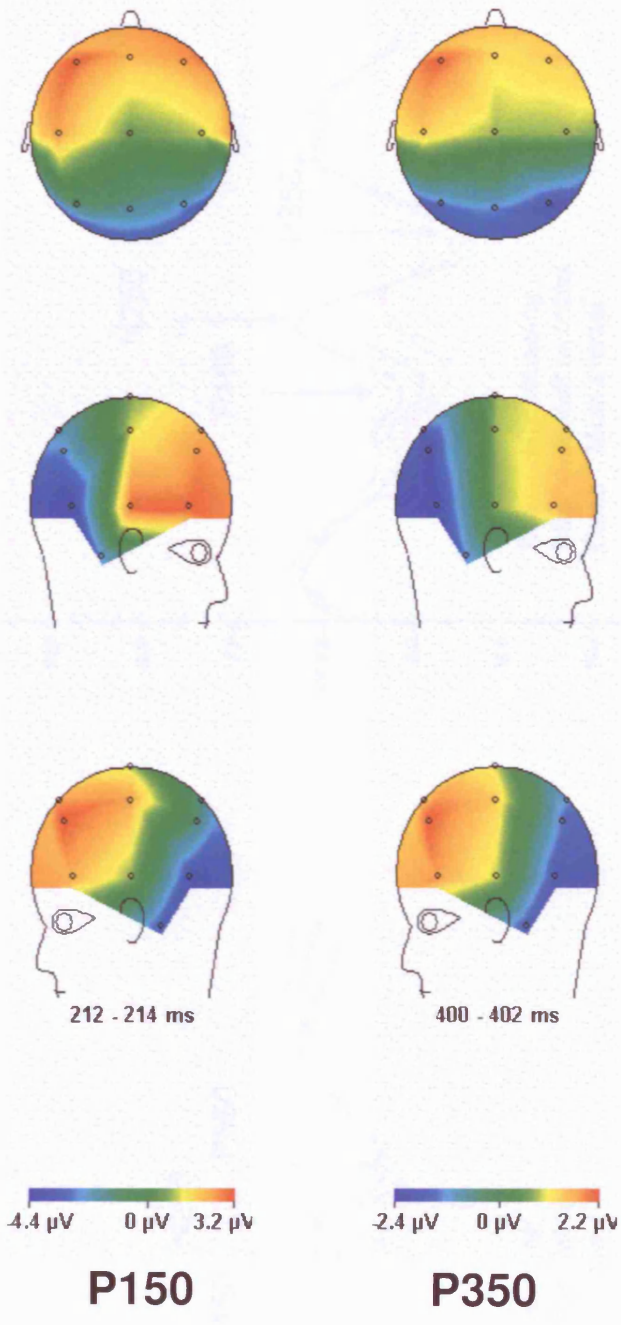


Figure 3.5. The amplitudes of the P150 and P350 of the group mean ERPs of the control group at 5-8 months show an inversion of the polarity in wakefulness and sleep across the anterior-posterior axis.

Figure 3.6

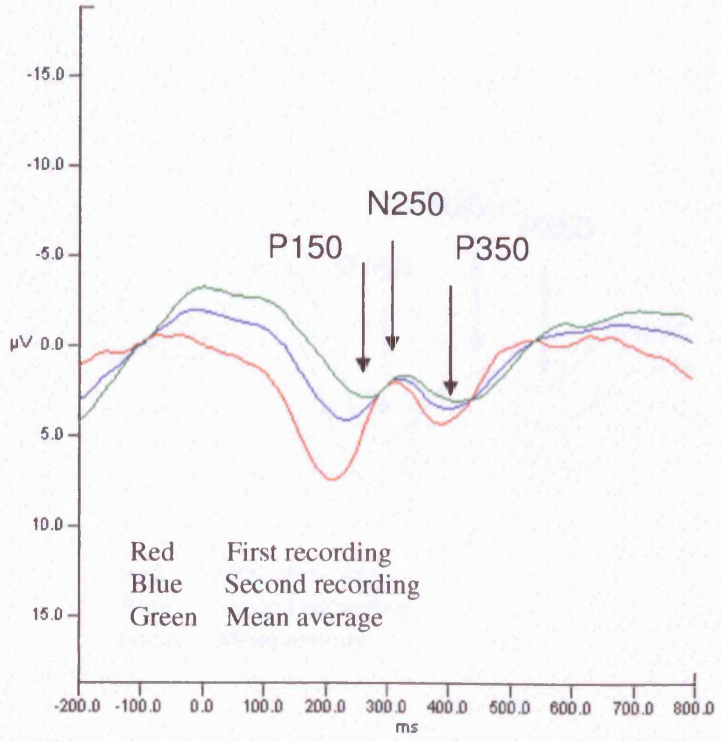
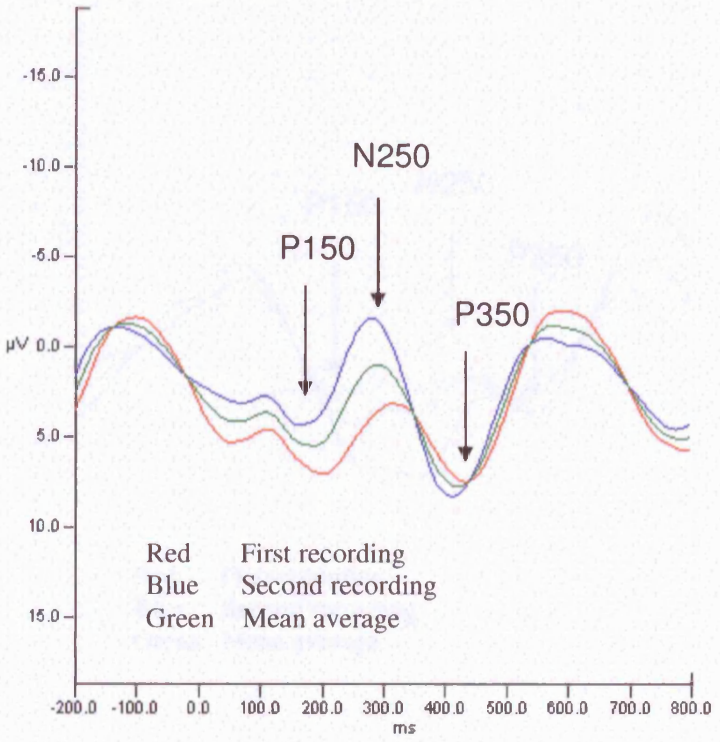


Figure 3.7



Figures 3.6 and 3.7 show the replicability of the obligatory components P150, N250 and P350 in 2 control infants during wakefulness in two consecutive recordings at electrode F3.

Figure 3.8

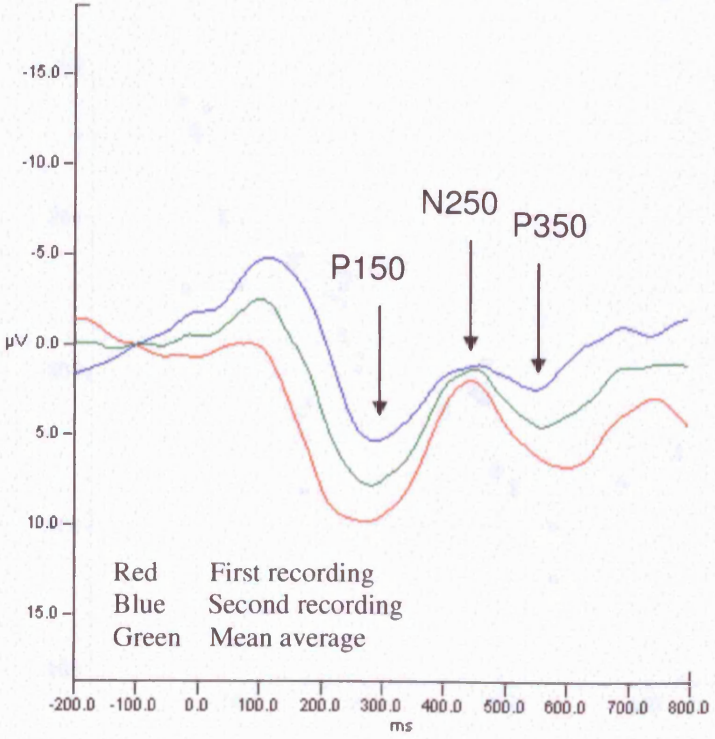
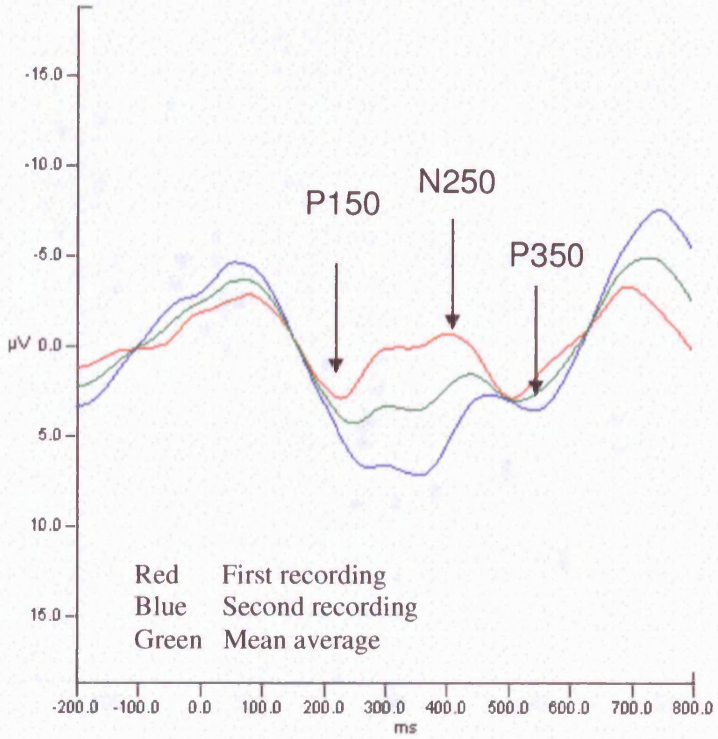


Figure 3.9



Figures 3.8 and 3.9 show the replicability of the obligatory components P150, N250 and P350 in 2 control infants during sleep in two consecutive recordings at electrode F3.

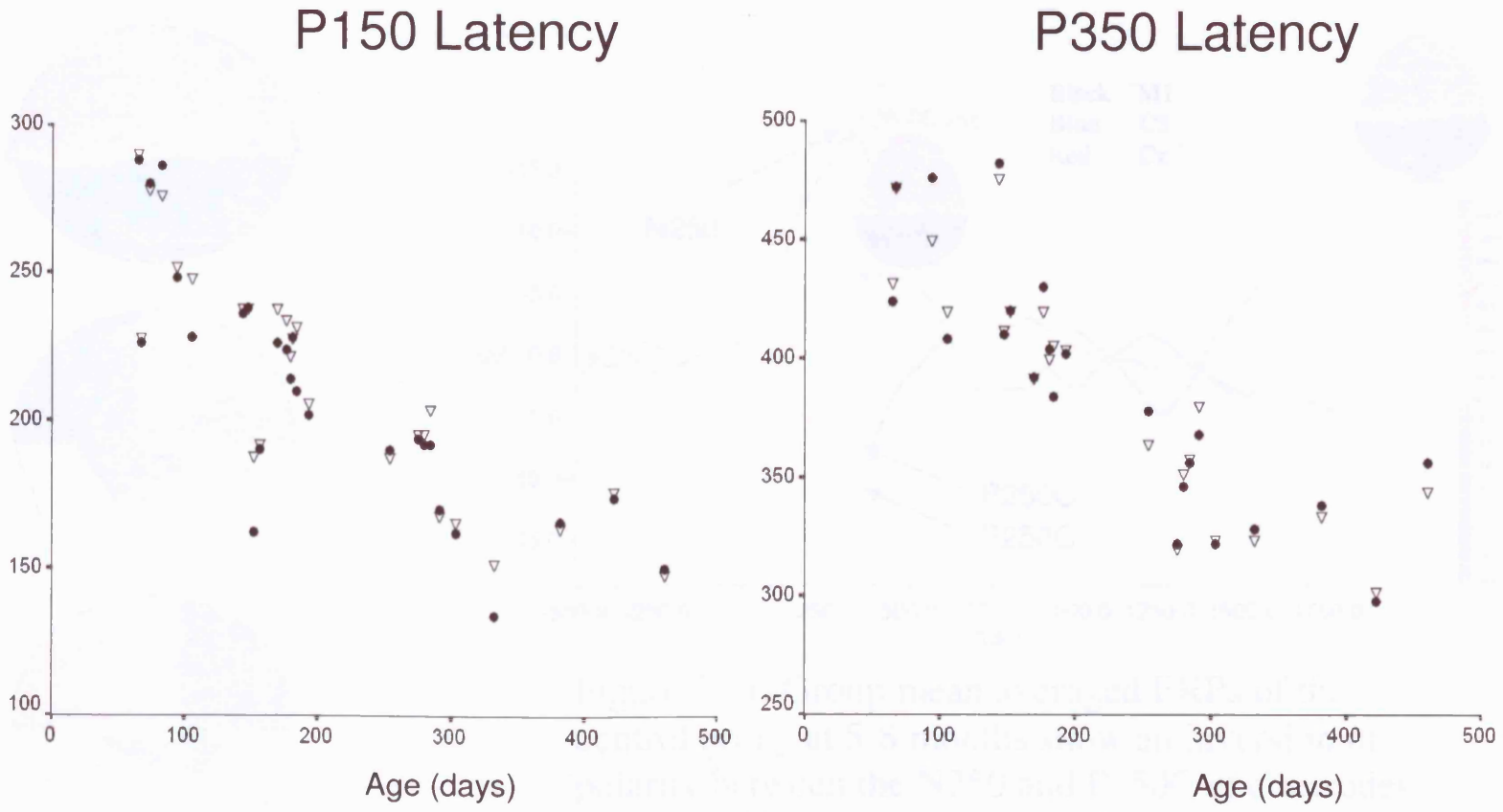
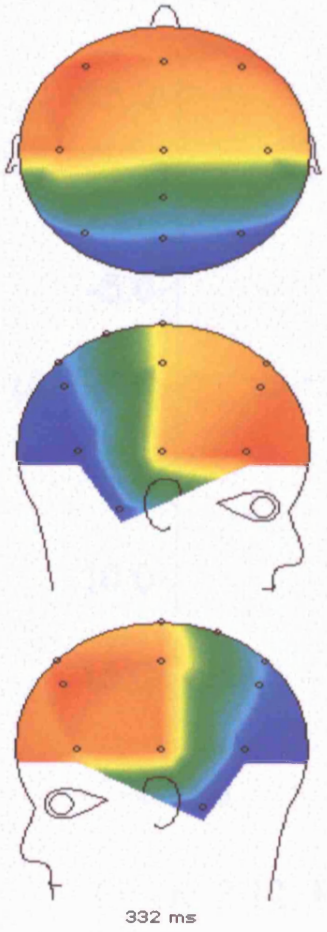


Figure 3.10 shows the latencies of the P150 and P350 in control infants corrected for gestational age during wakefulness at electrodes F3 (•) and F4 (∇).



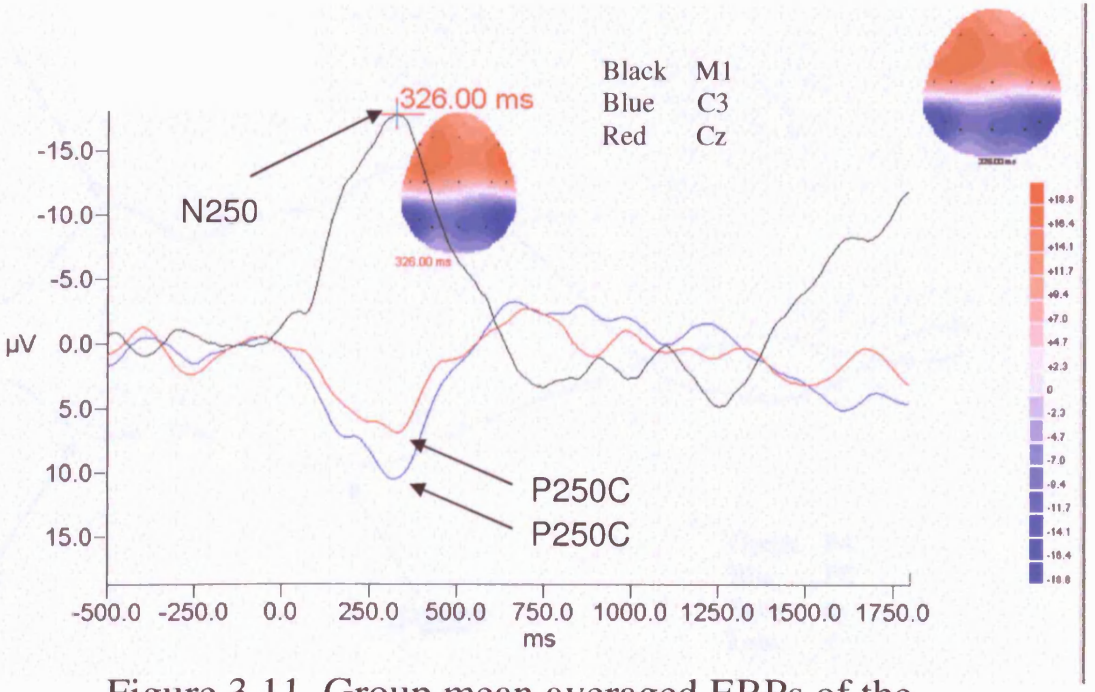


Figure 3.11. Group mean averaged ERPs of the control group at 5-8 months show an inversion of polarity between the N250 and P250C at electrodes M1 and C3 and Cz during wakefulness.

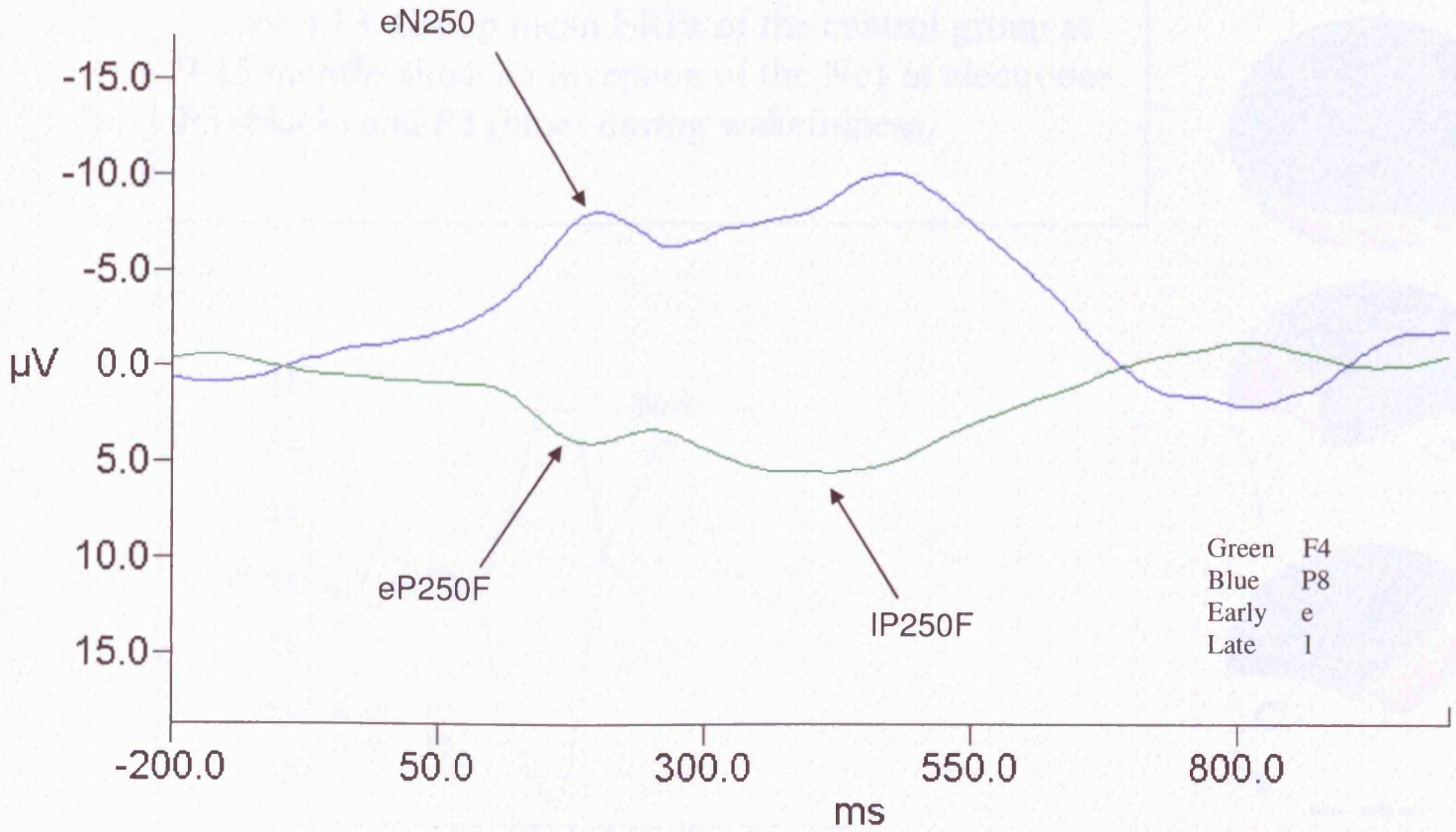
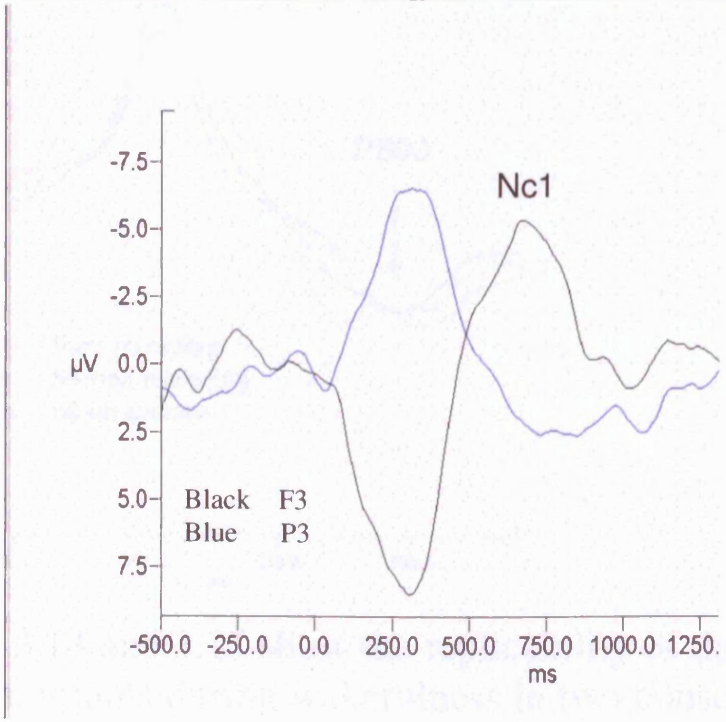


Figure 3.12. ERP of a control infant at 4 months shows the eP250F and lP250F at F4 and the inversion of polarity between the eP250F and the eN250 at P8.

Figure 3.13. Group mean ERPs of the control group at 9-15 months show an inversion of the Nc1 at electrodes F3 (black) and P3 (blue) during wakefulness.



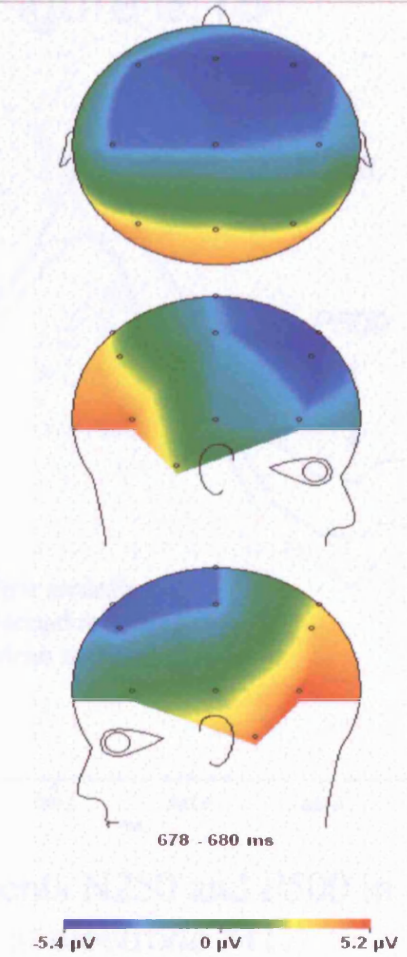


Figure 3.14

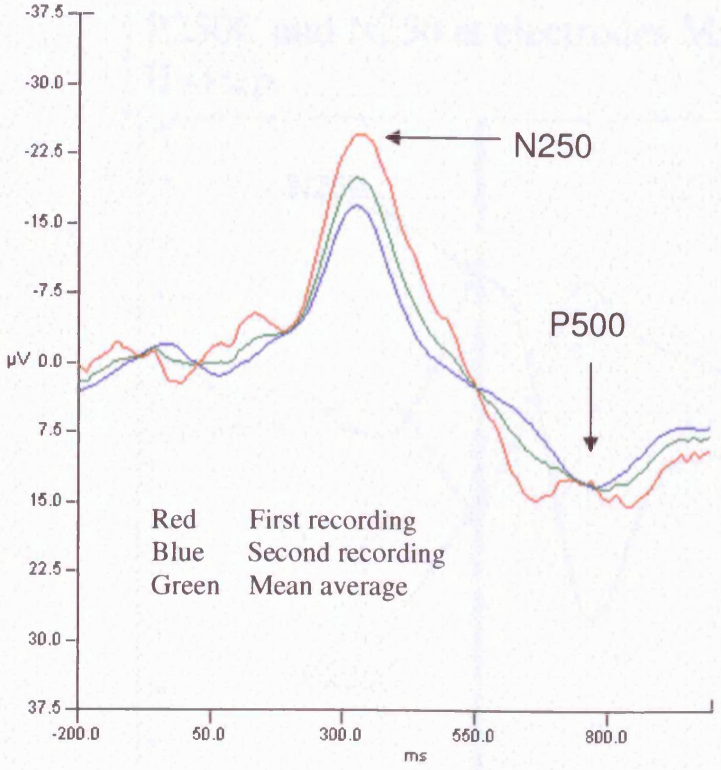
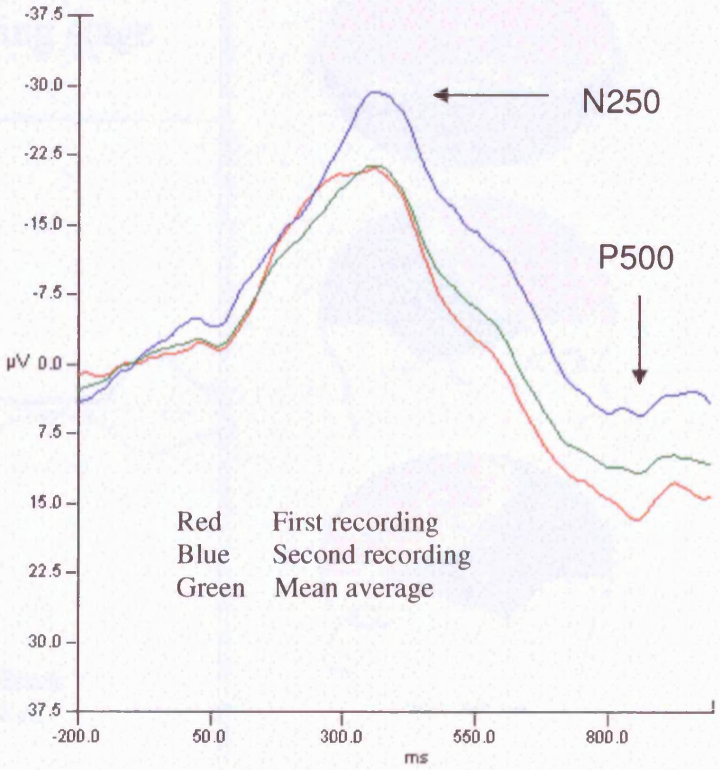
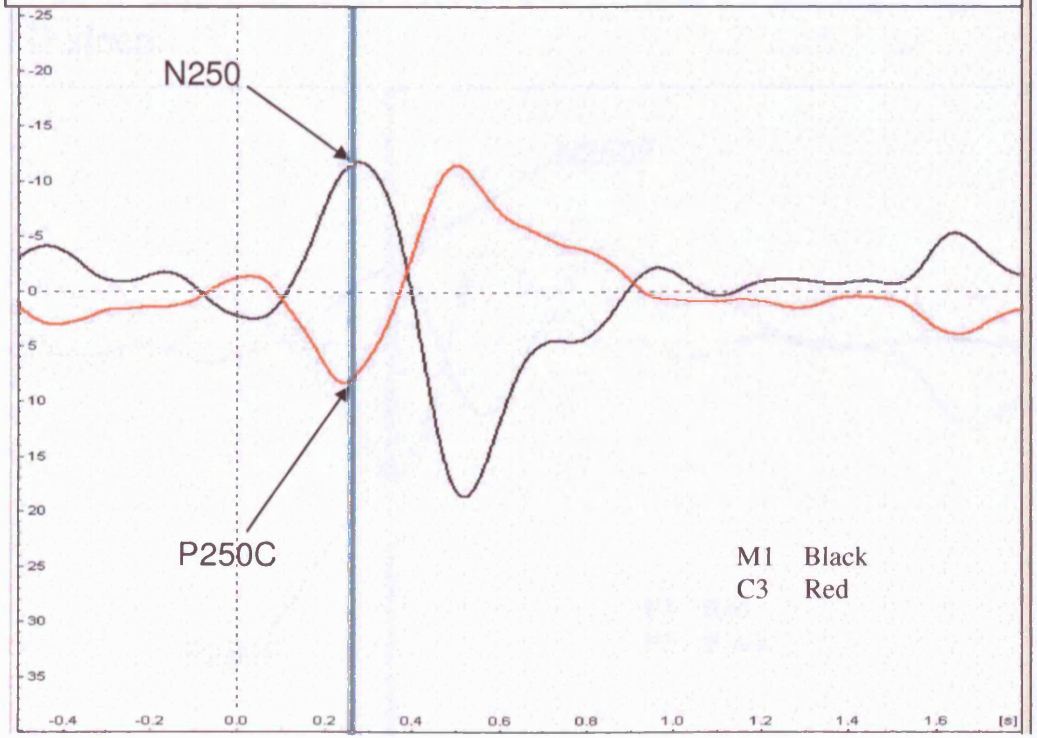


Figure 3.15



Figures 3.14 and 3.15 show the replicability of the novelty components N250 and P500 in 2 control infants during wakefulness in two consecutive recordings at electrode M1.

Figure 3.16. Group mean ERPs of the control group at 5-8 months show an inversion of polarity between the P250C and N250 at electrodes M1 and C3 during stage II sleep.



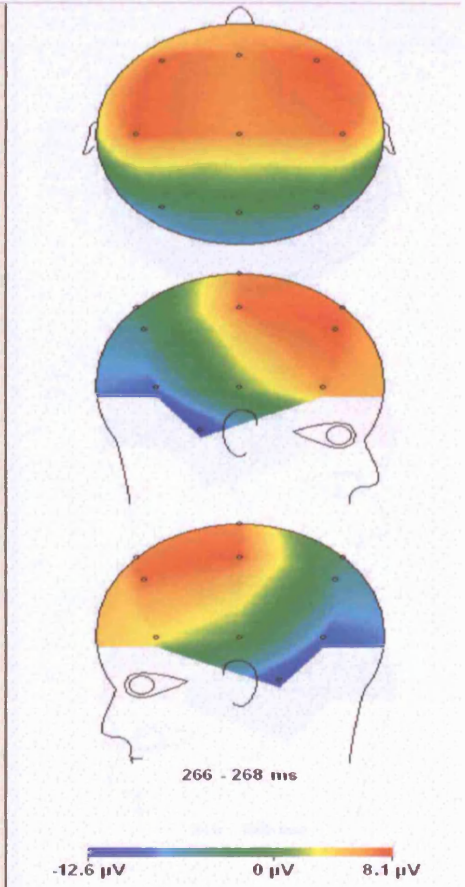
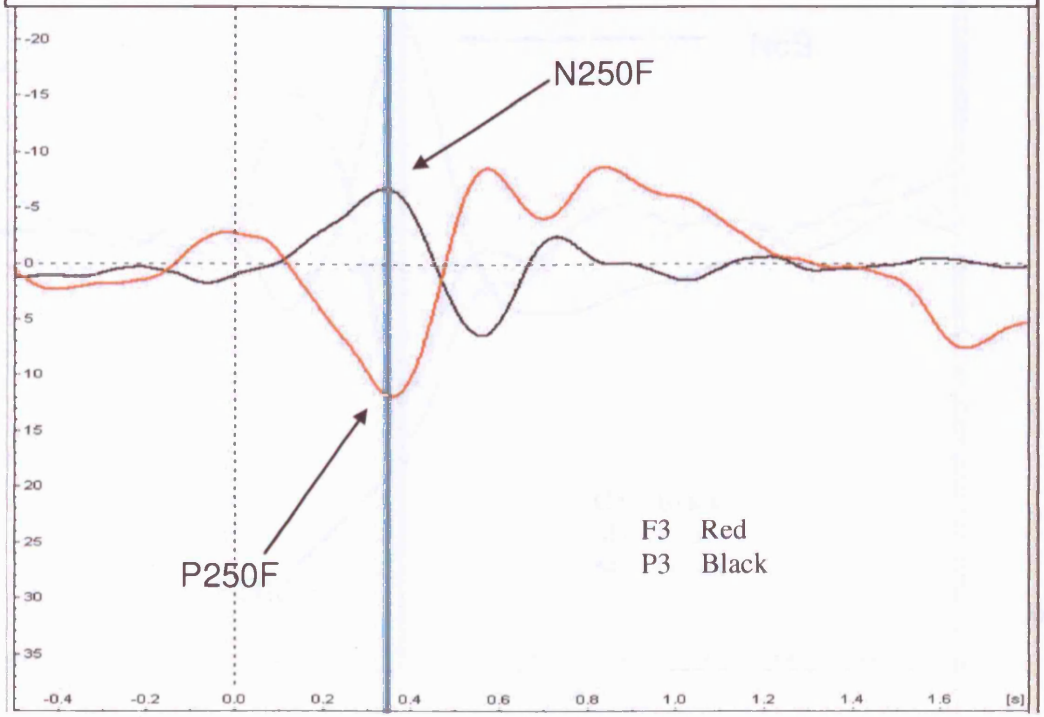


Figure 3.17. Group mean ERPs of the control group at 5-8 months show an inversion of polarity between the P250F and N250F at electrodes F3 and P3 during stage II sleep.



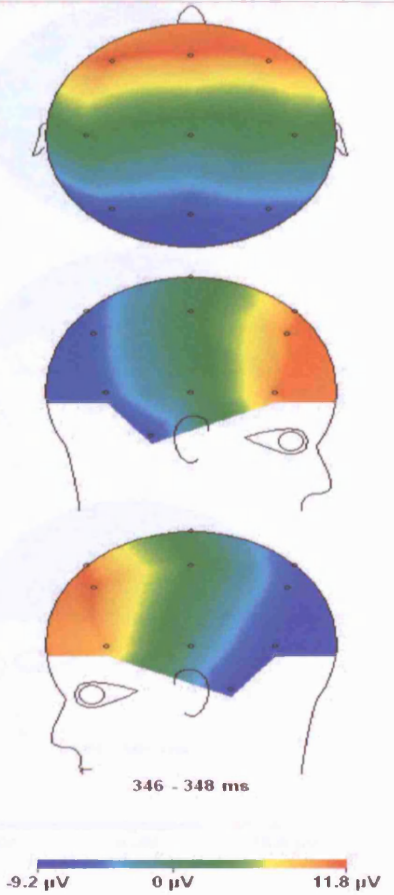
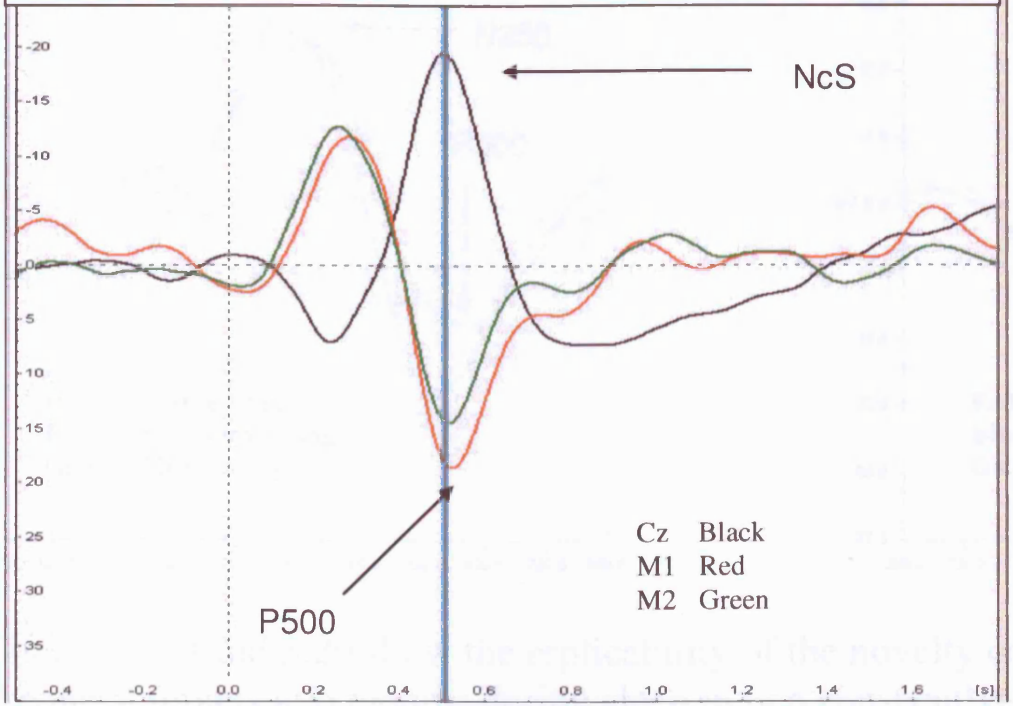


Figure 3.18. Group mean ERPs of the control group at 5-8 months show an inversion of polarity between P500 and NcS at electrodes Cz and M1/M2 during sleep.



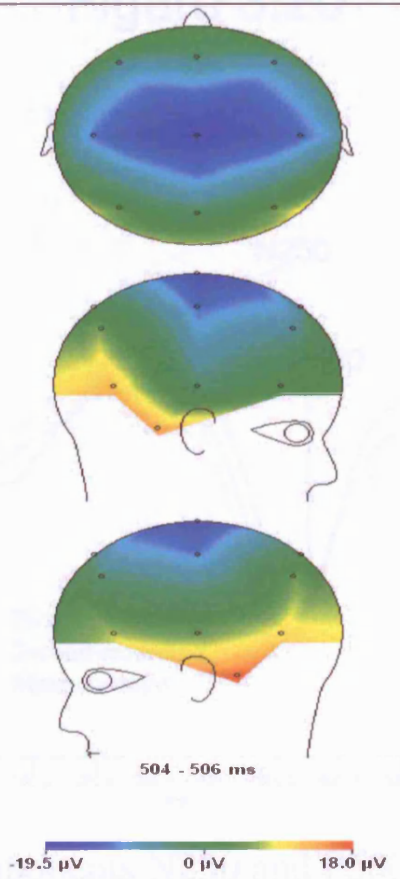


Figure 3.19

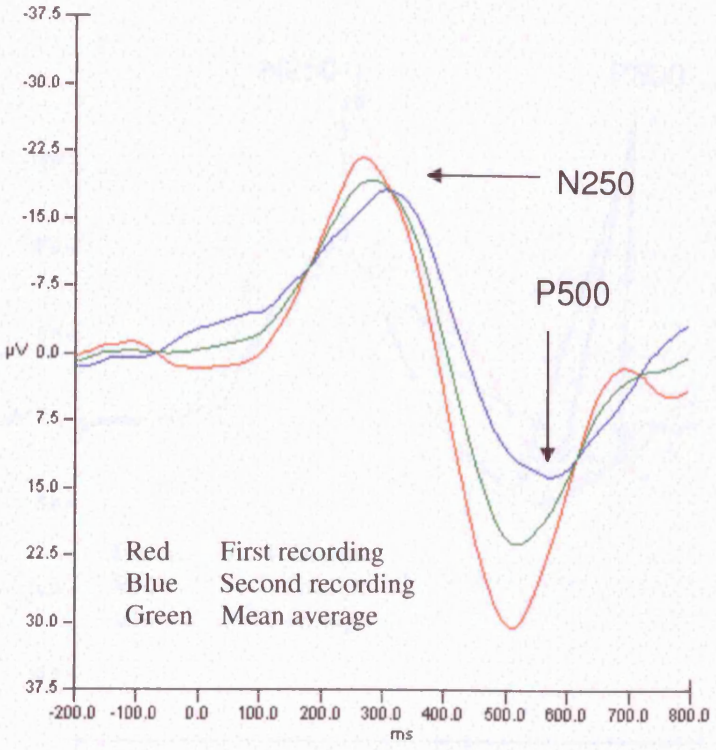
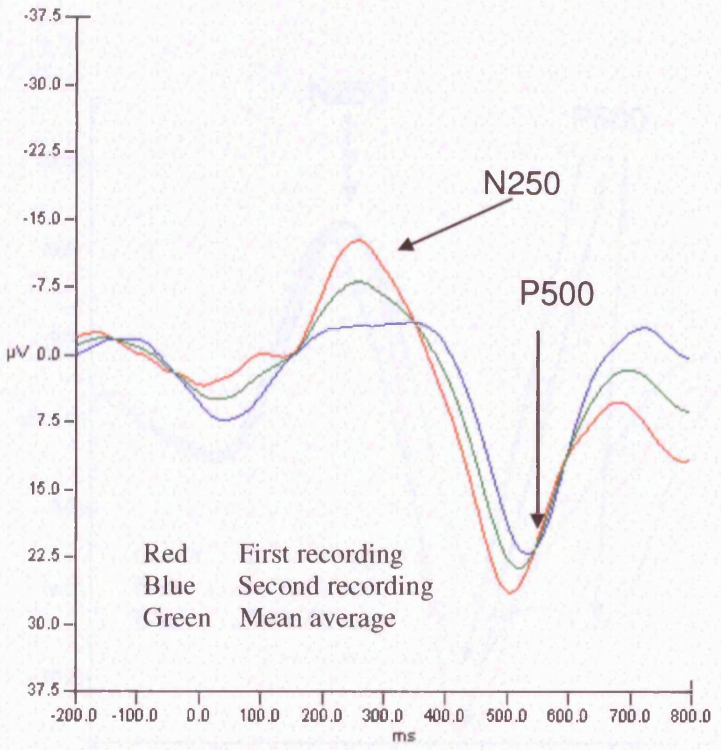


Figure 3.20



Figures 3.19 and 3.20 show the replicability of the novelty components N250 and P500 in 2 control infants at 6 months during sleep in two consecutive recordings at electrode M1.

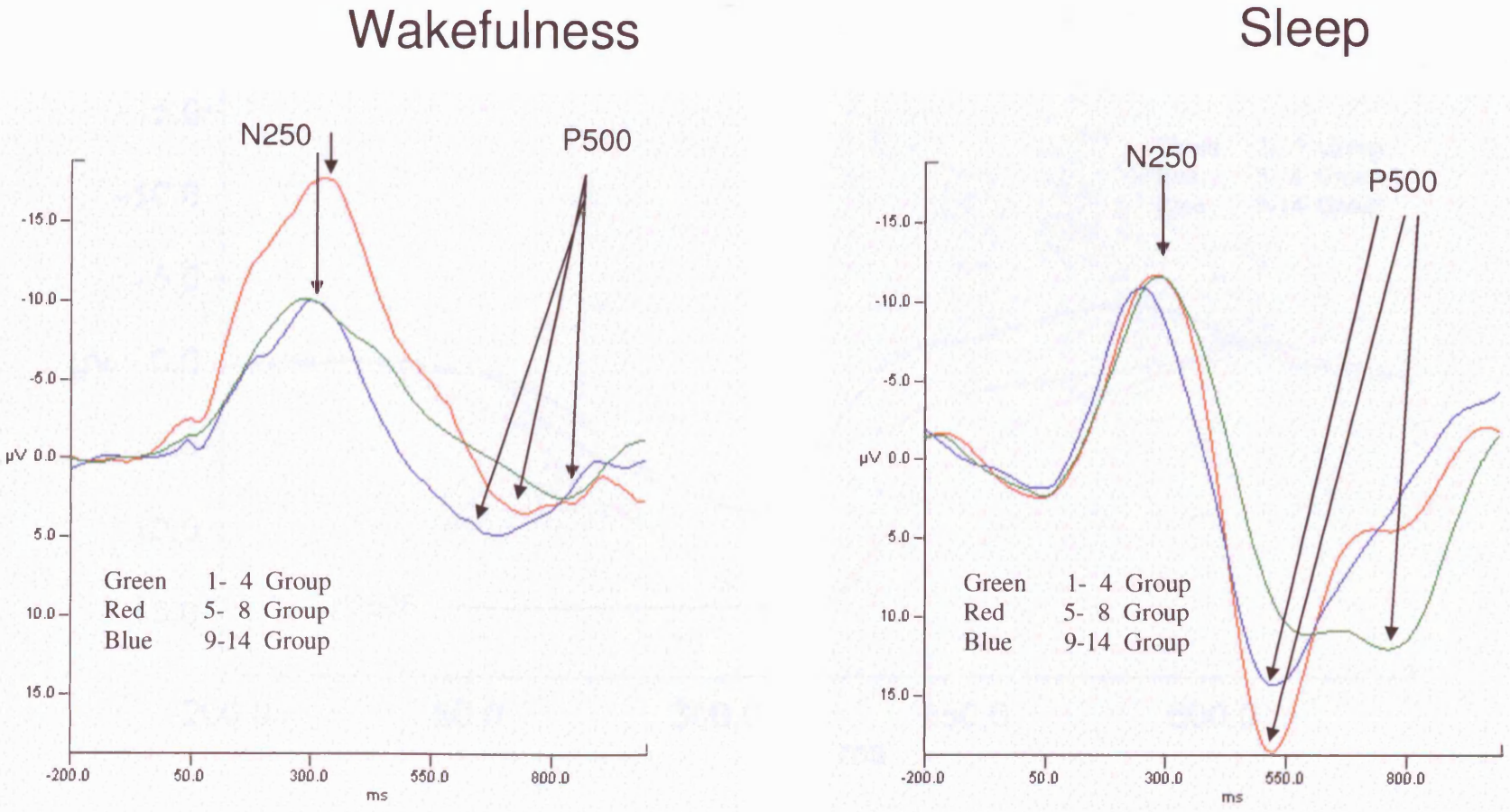


Figure 3.21. Group mean ERPs of the control groups at 1-4, 5-8 and 9-14 months show the N250 and P500 during wakefulness and sleep at electrode M1.

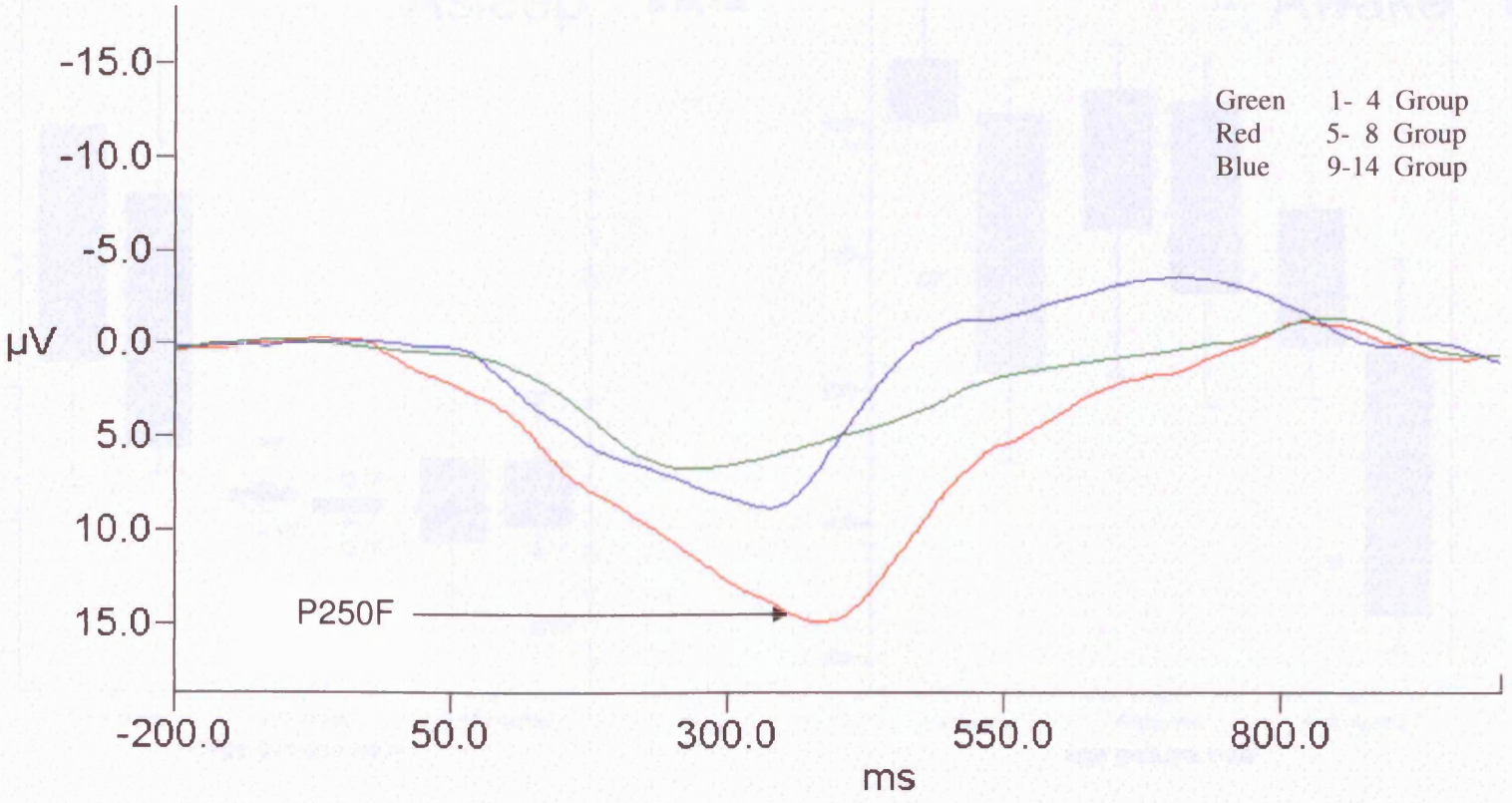


Figure 3.22. Group mean ERPs of the control groups at 1-4, 5-8, 9-14 months show the P250F at F4 during wakefulness.

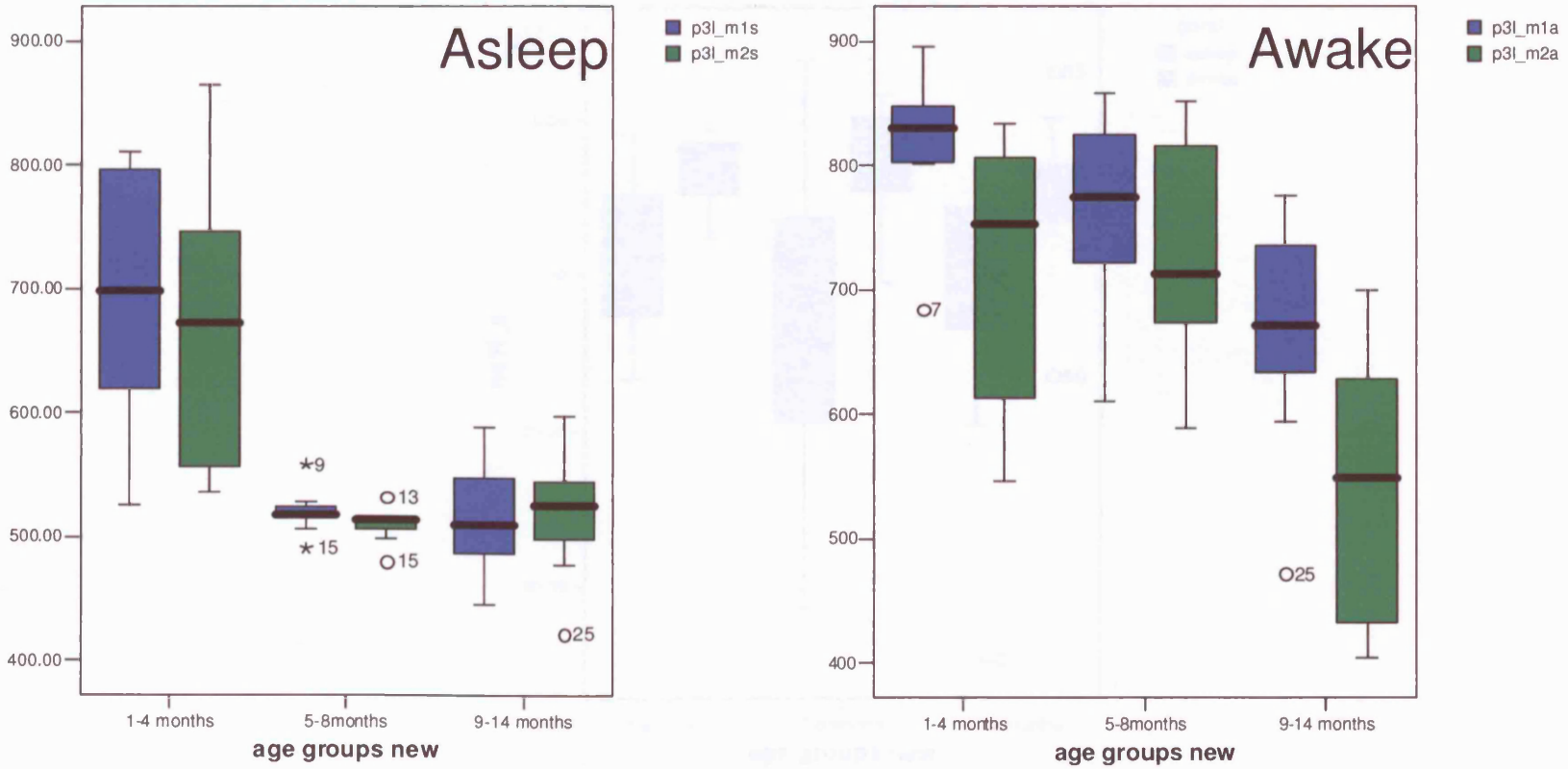


Figure 3.23 Box and whisker plots show the P500 latency at left (M1) and right (M2) mastoid electrodes of the control groups at 1-4, 5-8 and 9-14 months during sleep (s) and wakefulness (a).

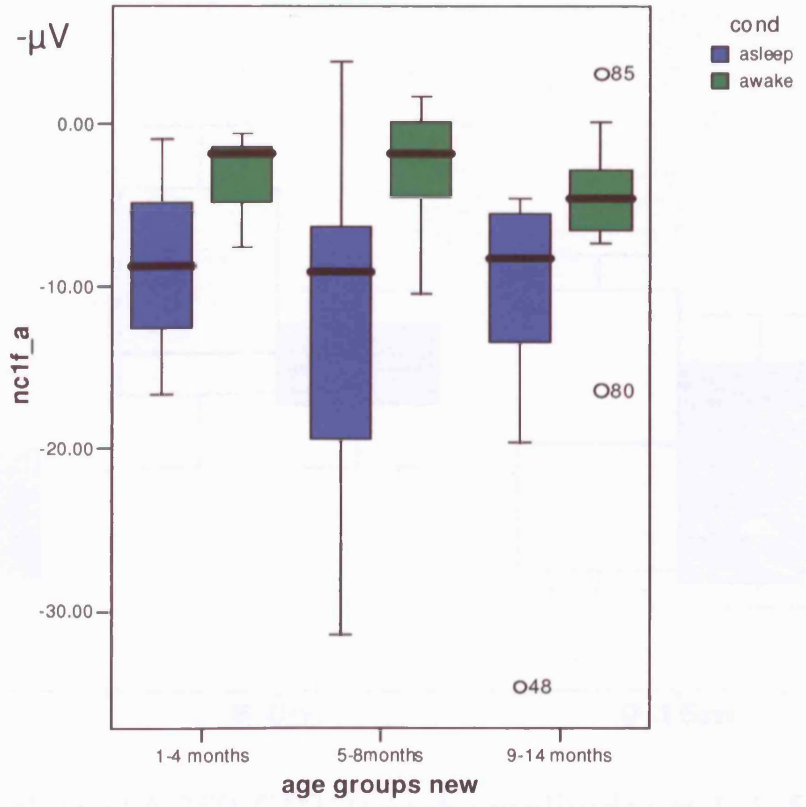


Figure 3.24. Box and whisker plots show the fNc1amplitudes of the control groups at 1-4, 5-8 and 9-15 months at electrode F3 during sleep and wakefulness.

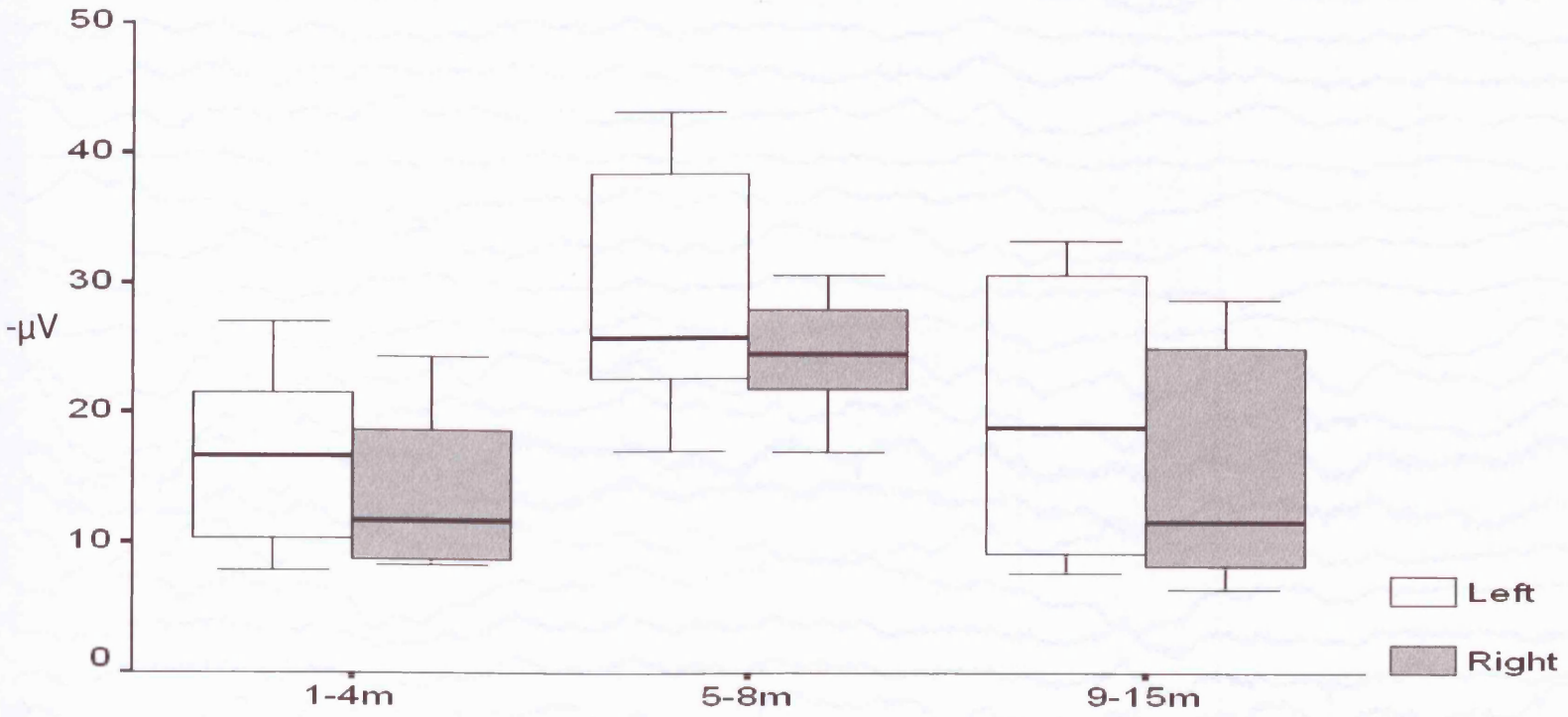


Figure 3.25 shows box plots of N250-CP250 peak amplitudes at 1-4, 5-8 and 9-15

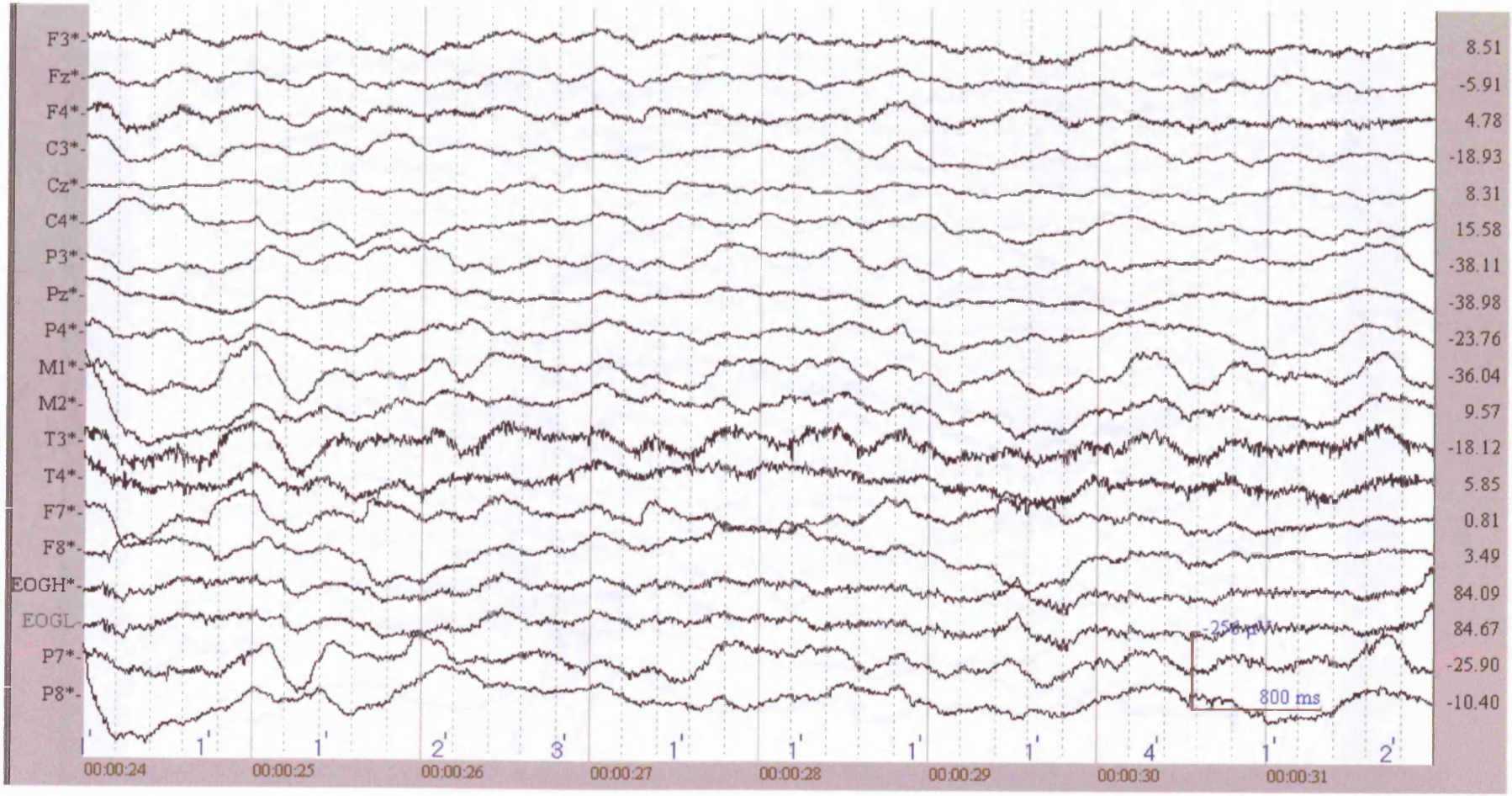


Figure 3.26. Moderate EEG abnormality during wakefulness showing widespread slowing of the background activity without focal signs or epileptiform features.

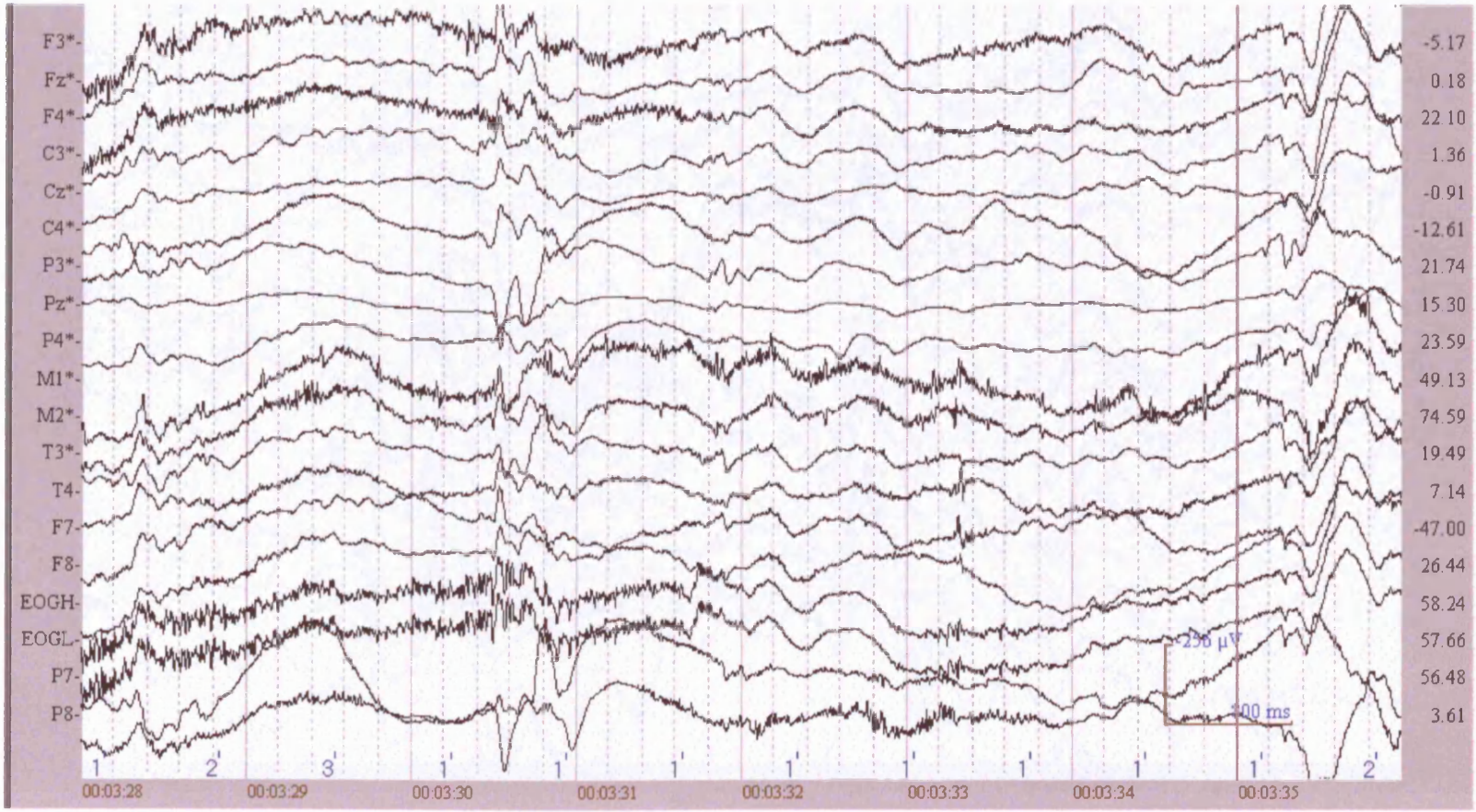


Figure 3.27. Severe EEG abnormality during wakefulness showing marked excess of slow activity and generalised spikes and waves.

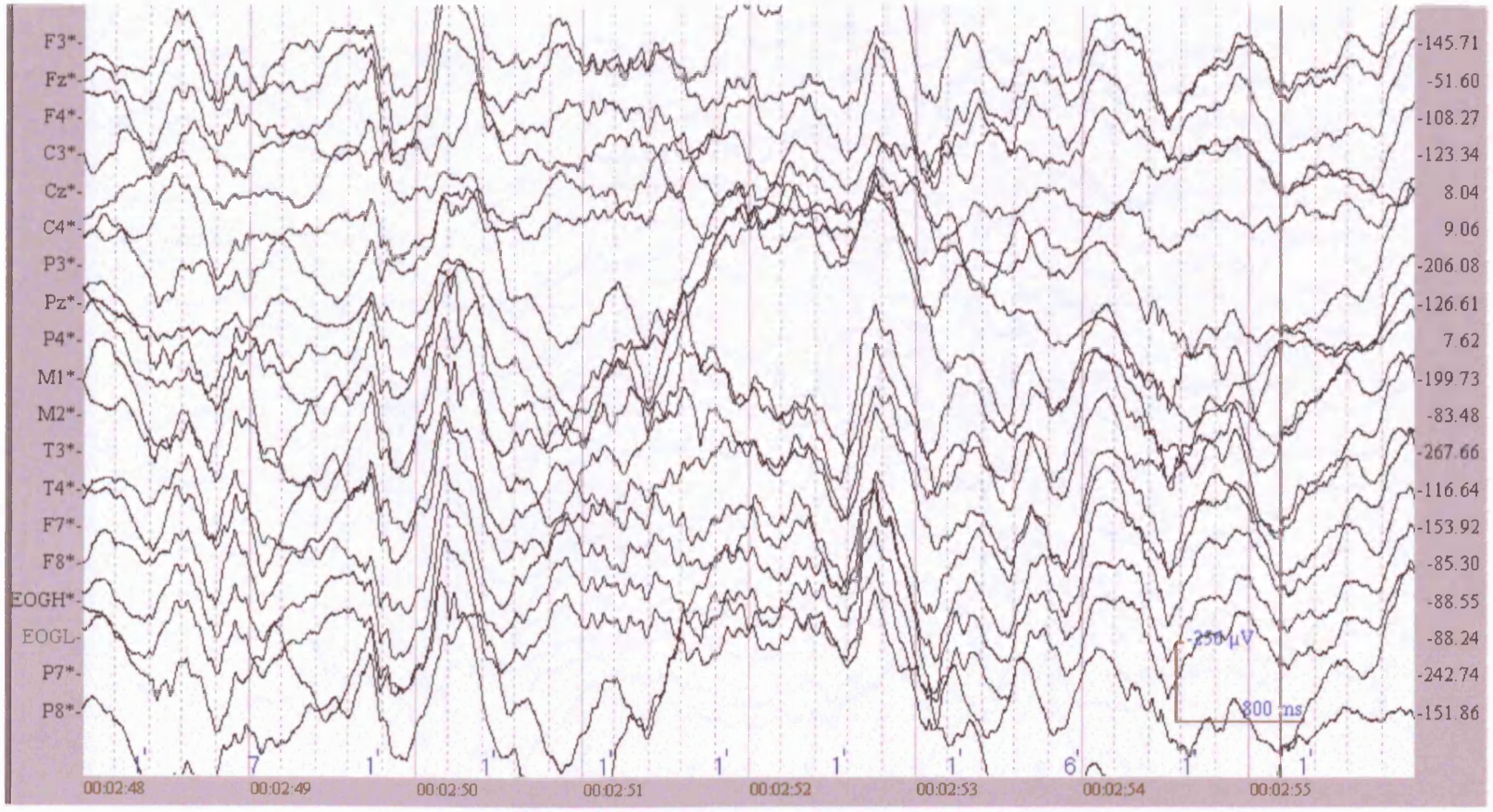


Figure 3.28. Moderate EEG abnormality during sleep showing K-complexes and sleep spindles indicating Stage 2 sleep. In addition there is an excess of slow activity for this state.

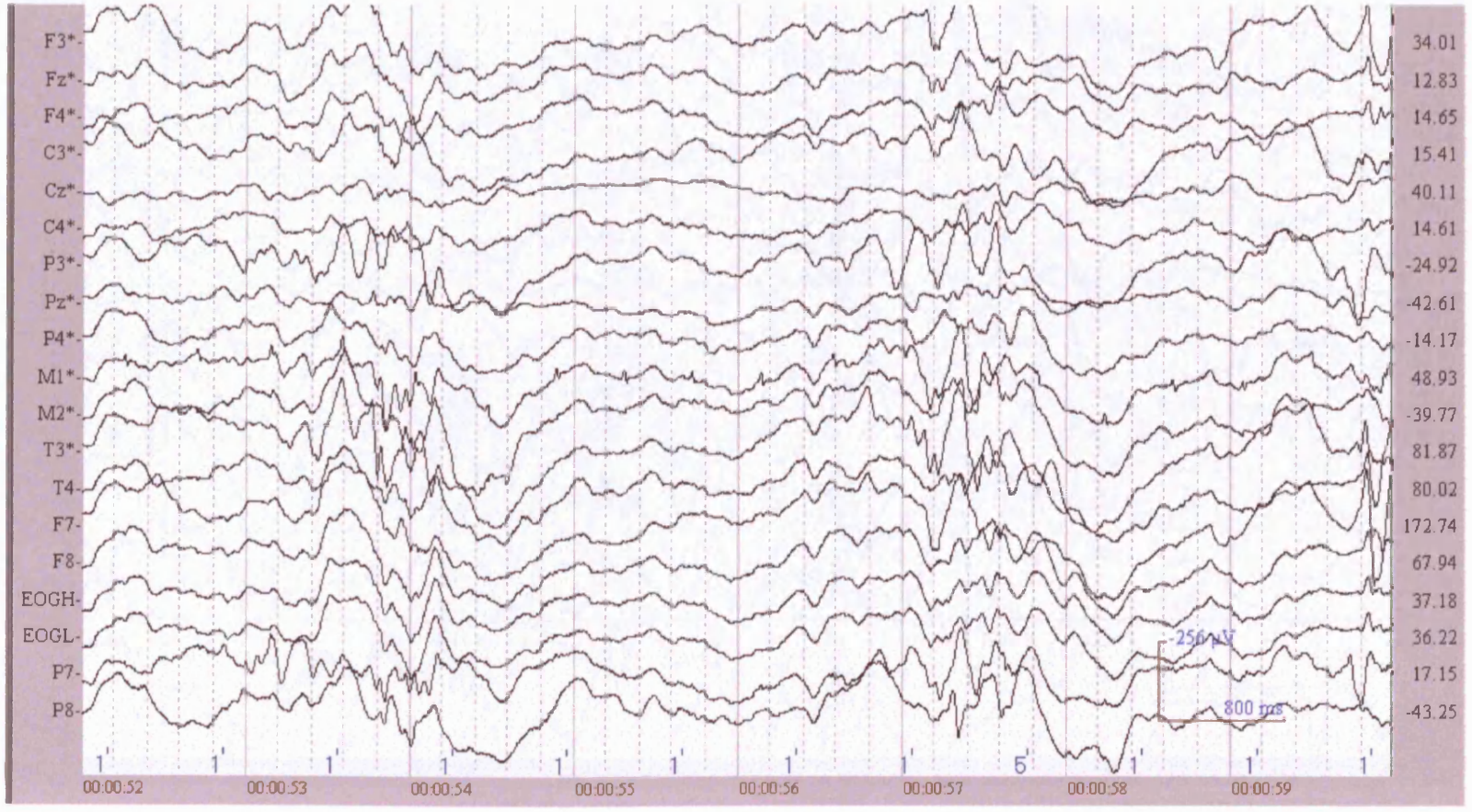


Figure 3.29. Severe EEG abnormality during sleep showing marked slow activity and bursts of discharges. No normal sleep architecture is seen.

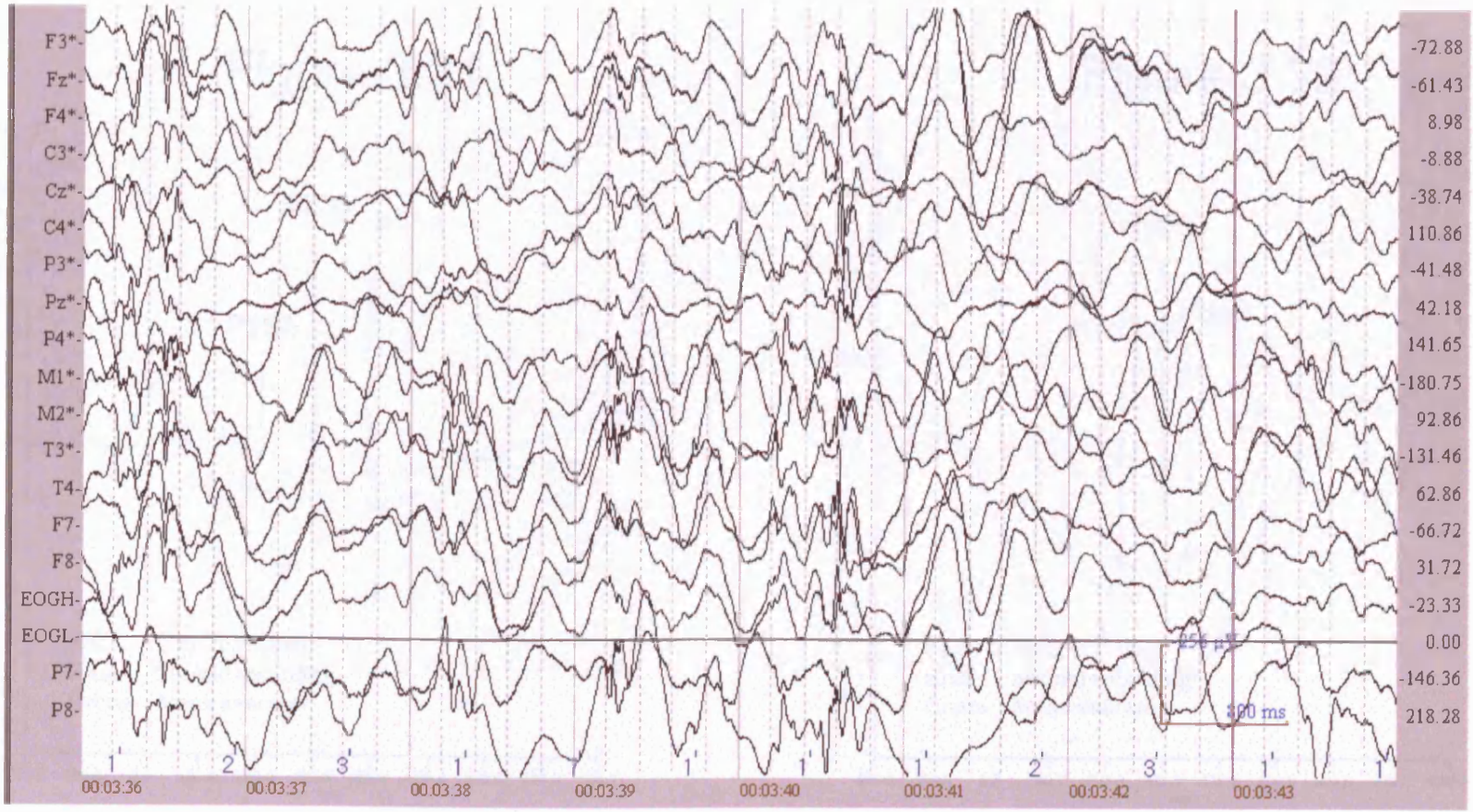


Figure 3.30. Hypsarrhythmia during sleep.

Figure 3.31

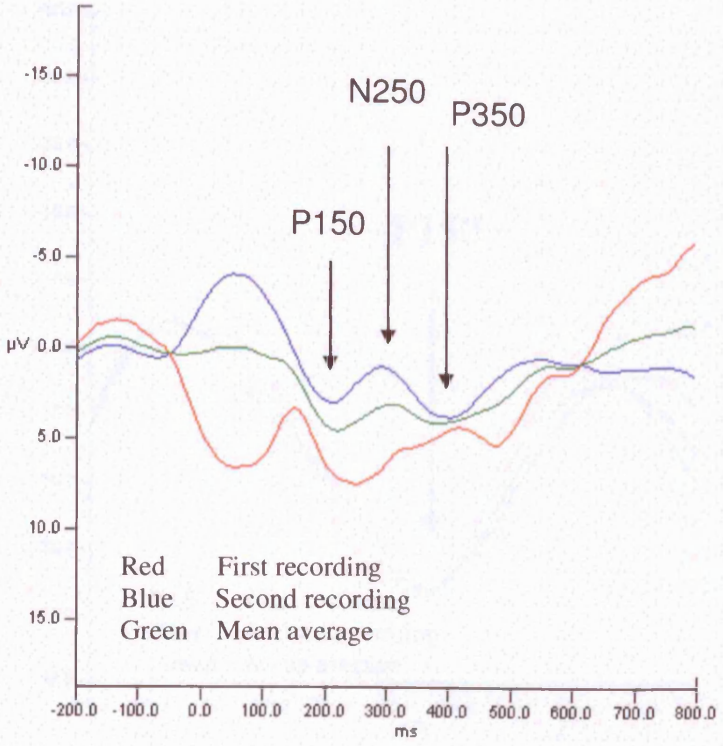
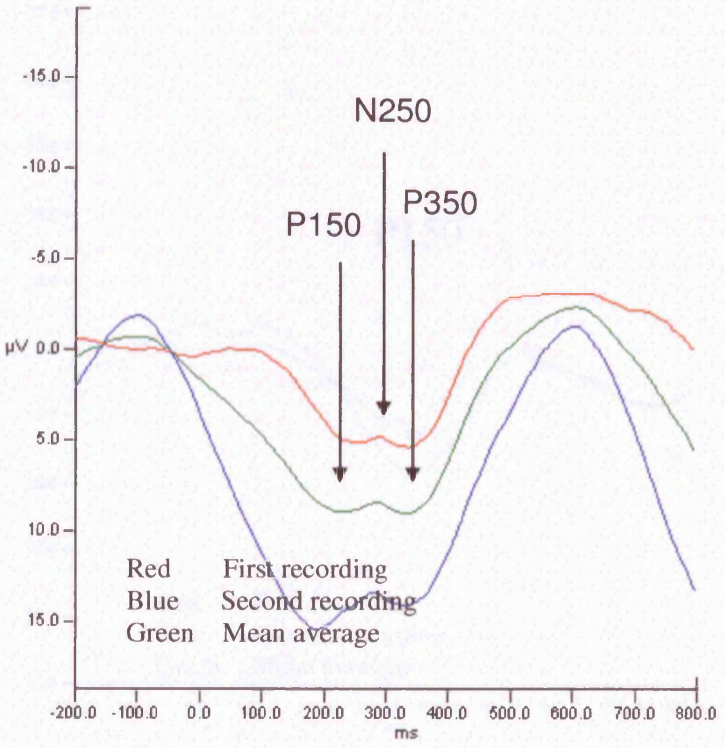


Figure 3.32



Figures 3.31 and 3.32 show the replicability of the P150, N250 and P350 in 2 infants with infantile spasms of 5-8 months during wakefulness in two consecutive recordings at electrode F3.

Figure 3.33

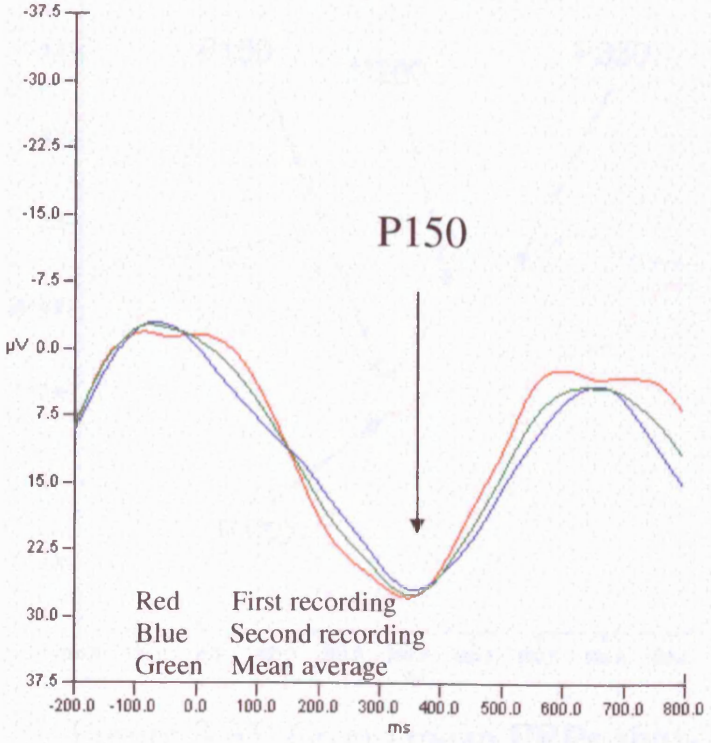
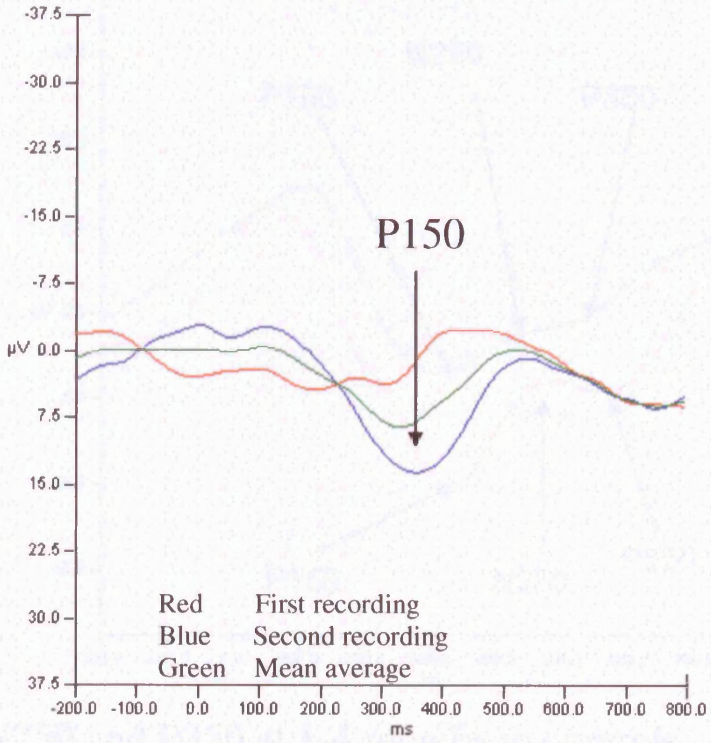


Figure 3.34



Figures 3.33 and 3.34 show the replicability of the P150 in 2 infants with infantile spasms of 5-8 months during sleep in two consecutive recordings at electrode F3.

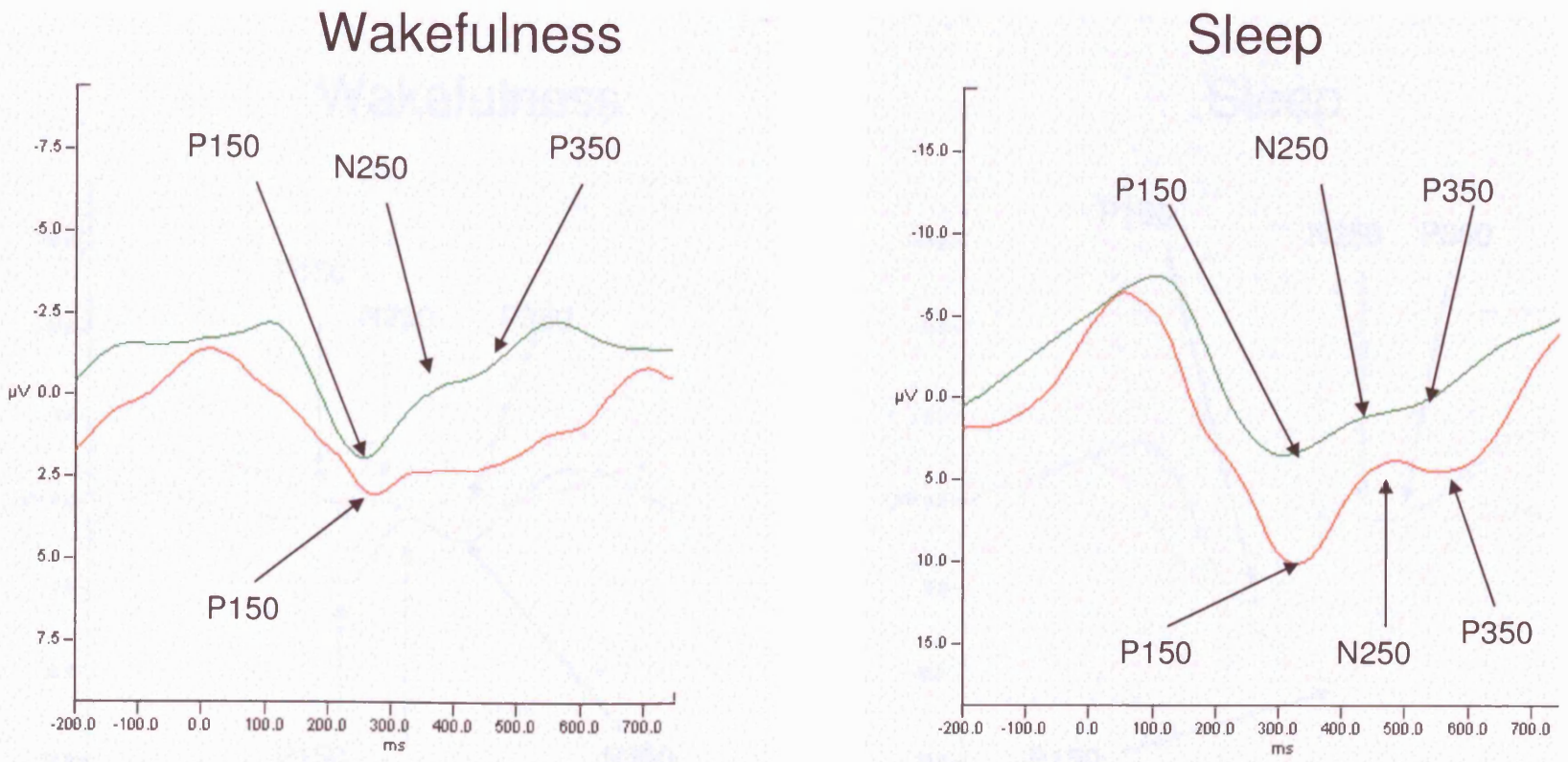


Figure 3.35. Group mean ERPs show the P150, N250 and P350 at 1-4 months in controls (green) and infants with IS (red) during wakefulness and sleep at electrode F3.

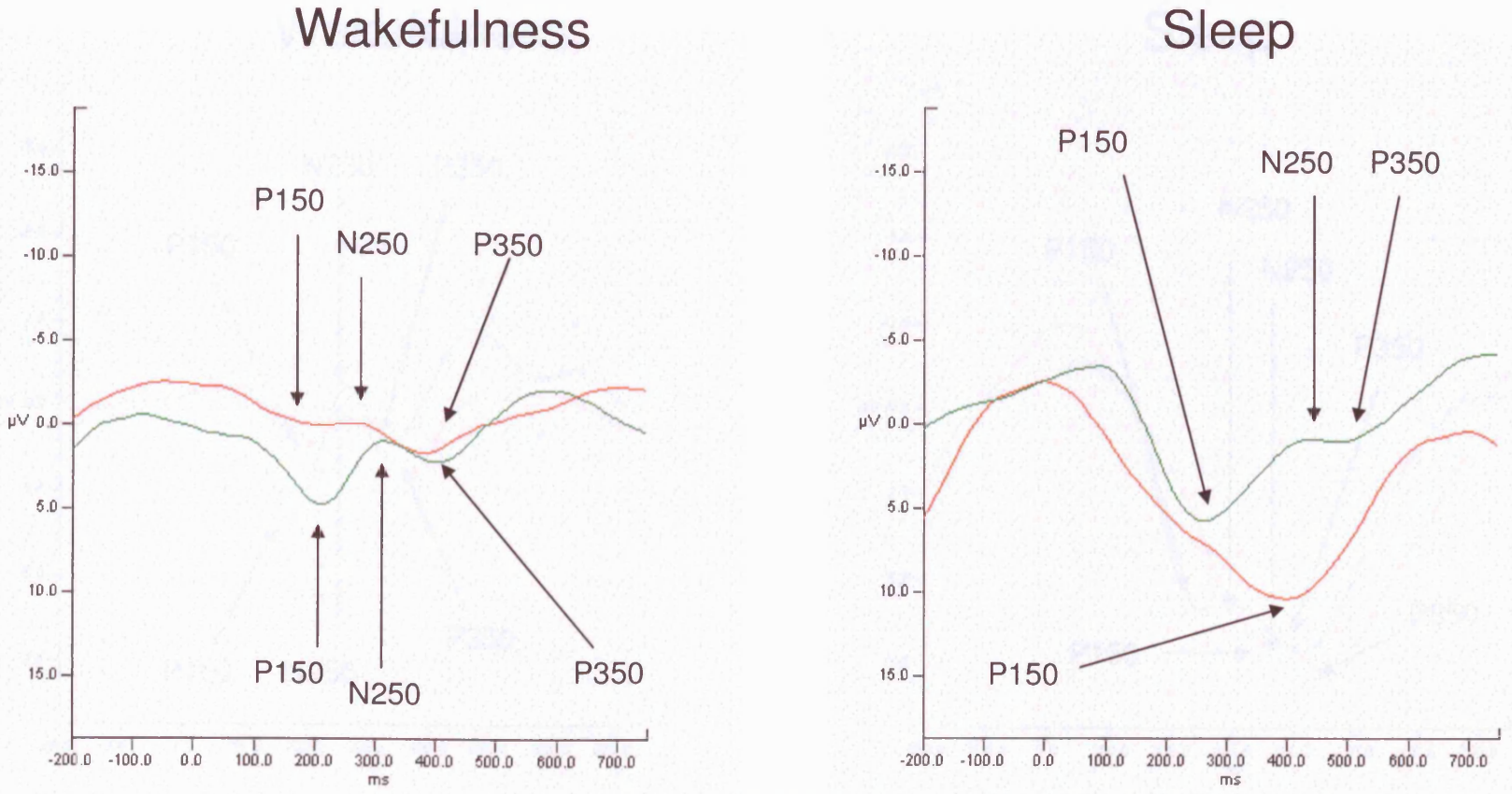


Figure 3.36. Group mean ERPs show the P150, N250 and P350 at 5-8 months in controls (green) and infants with IS during wakefulness and sleep at Electrode F3.

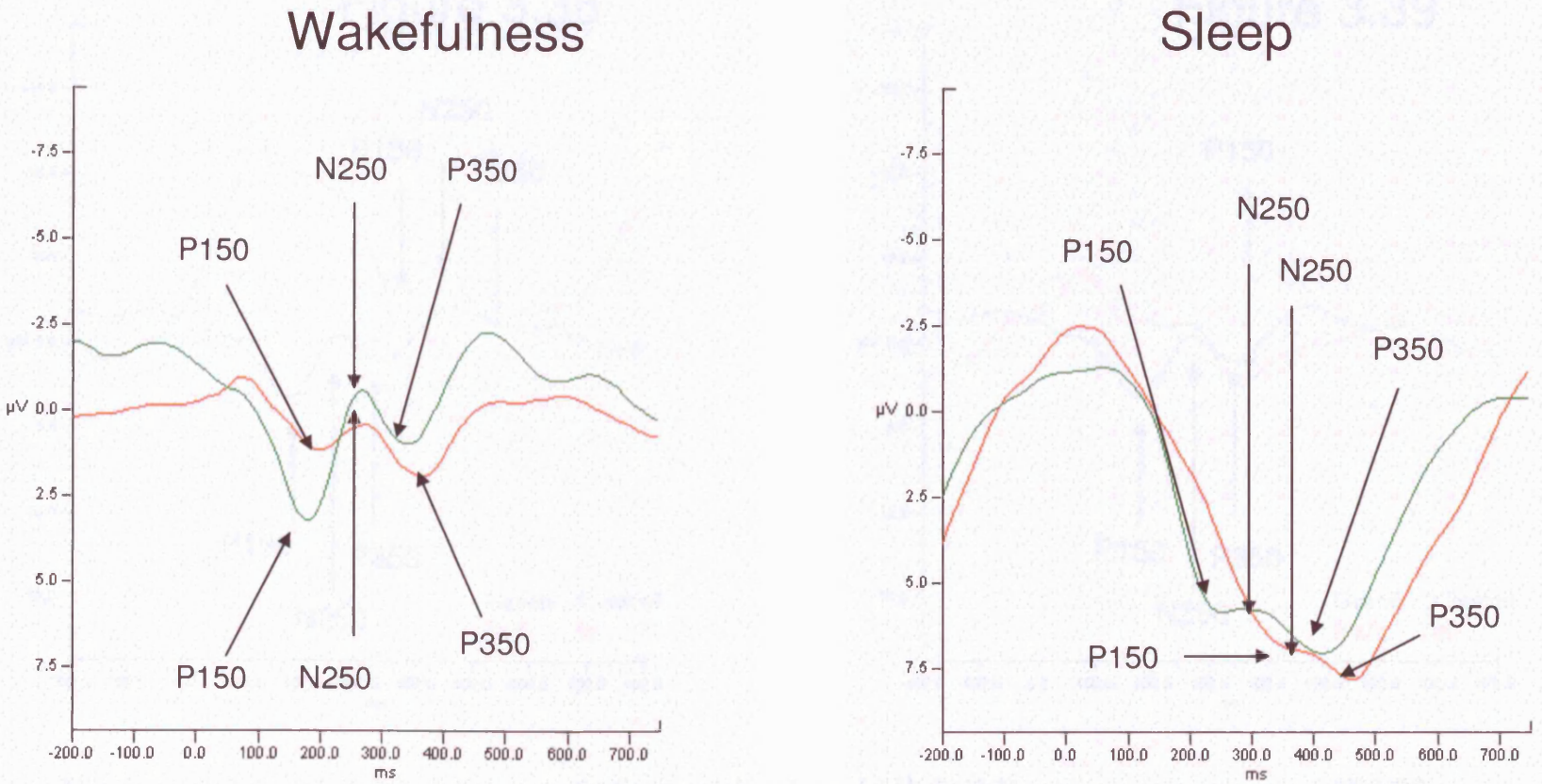


Figure 3.37. Group mean ERPs show the P150, N250 and P350 at 9-14 months in controls (green) and infants with IS (red) during wakefulness and sleep and electrode F3.

Figure 3.38

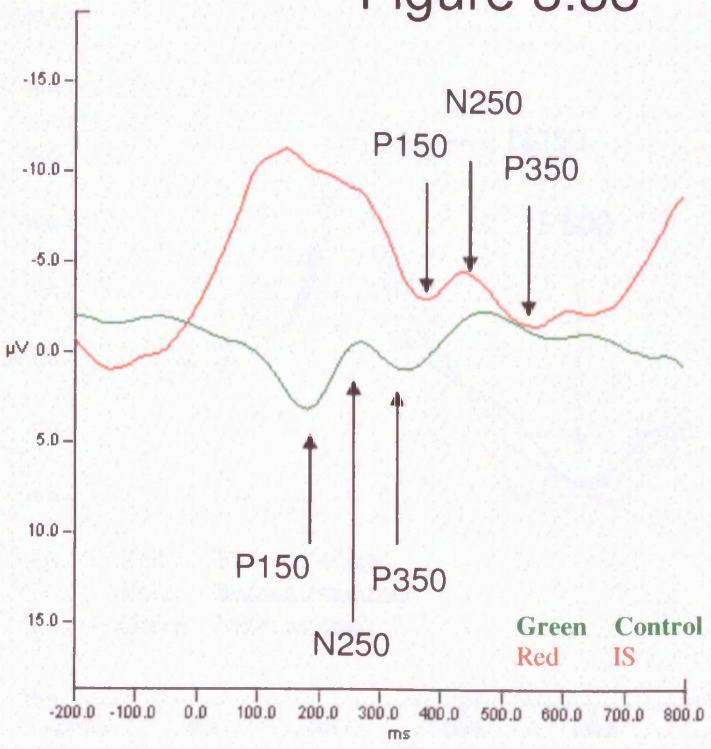
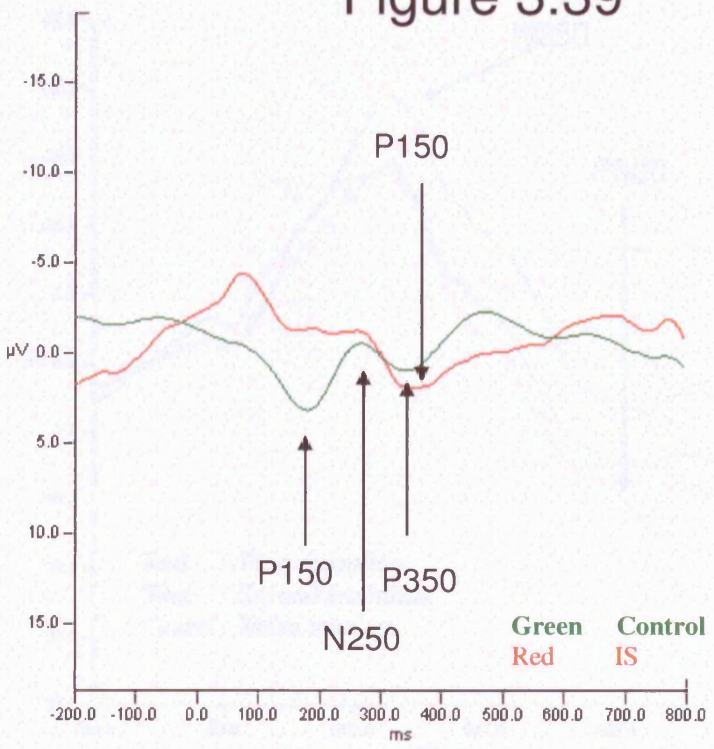


Figure 3.39



Figures 3.38 and 3.39 show one infant with IS and all 3 obligatory components (P150, N250, P350) and one infant with IS with only one component (P150) respectively during wakefulness compared to the group mean ERPs of the control group at 9-14 months.

Figure 3.40

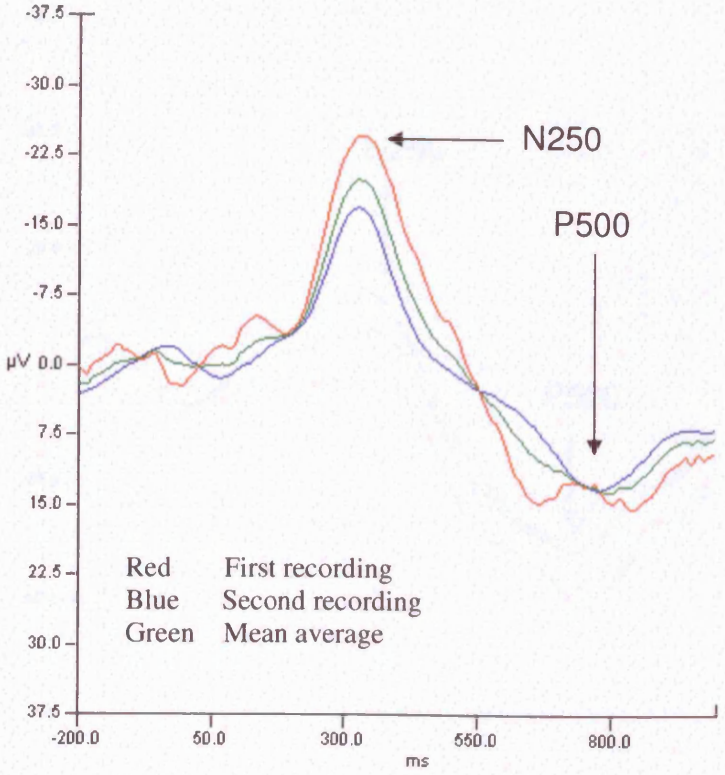
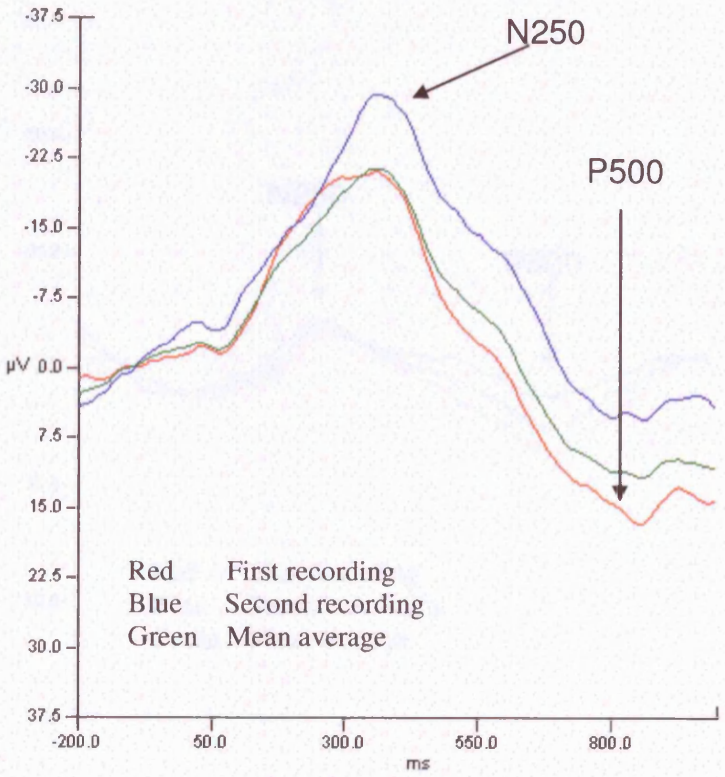


Figure 3.41



Figures 3.40 and 3.41 show the replicability of the novelty components N250 and P500 in 2 infants with IS of 5-8 months during wakefulness in two consecutive recordings at electrode M1.

Figure 3.42

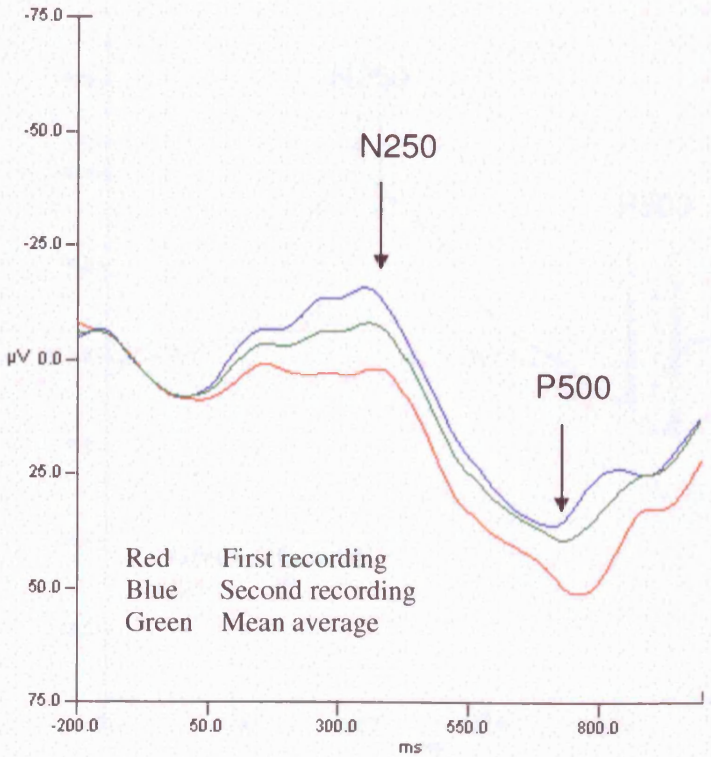
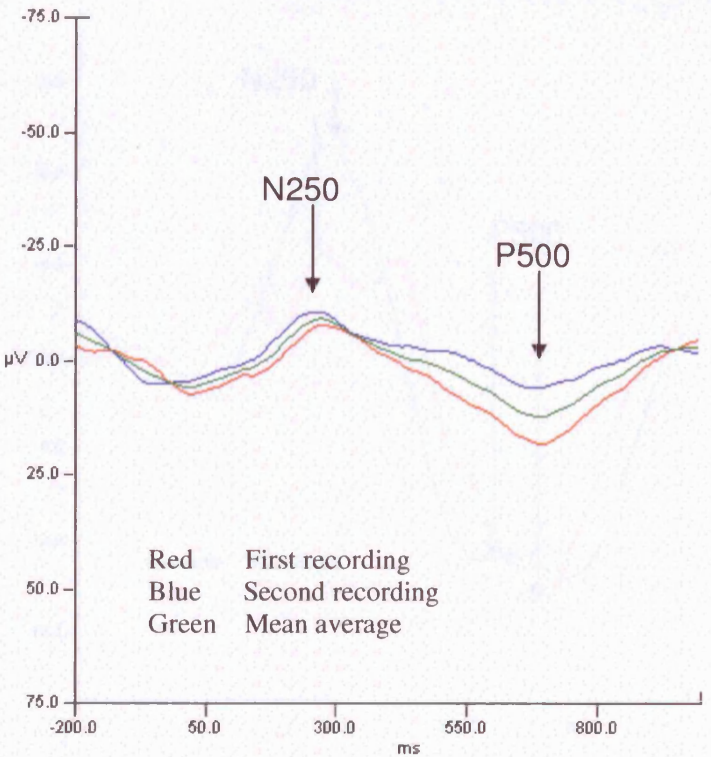


Figure 3.43



Figures 3.42 and 3.43 show the replicability of the novelty components N250 and P500 in 2 infants with IS during sleep in two consecutive recordings at electrode M1.

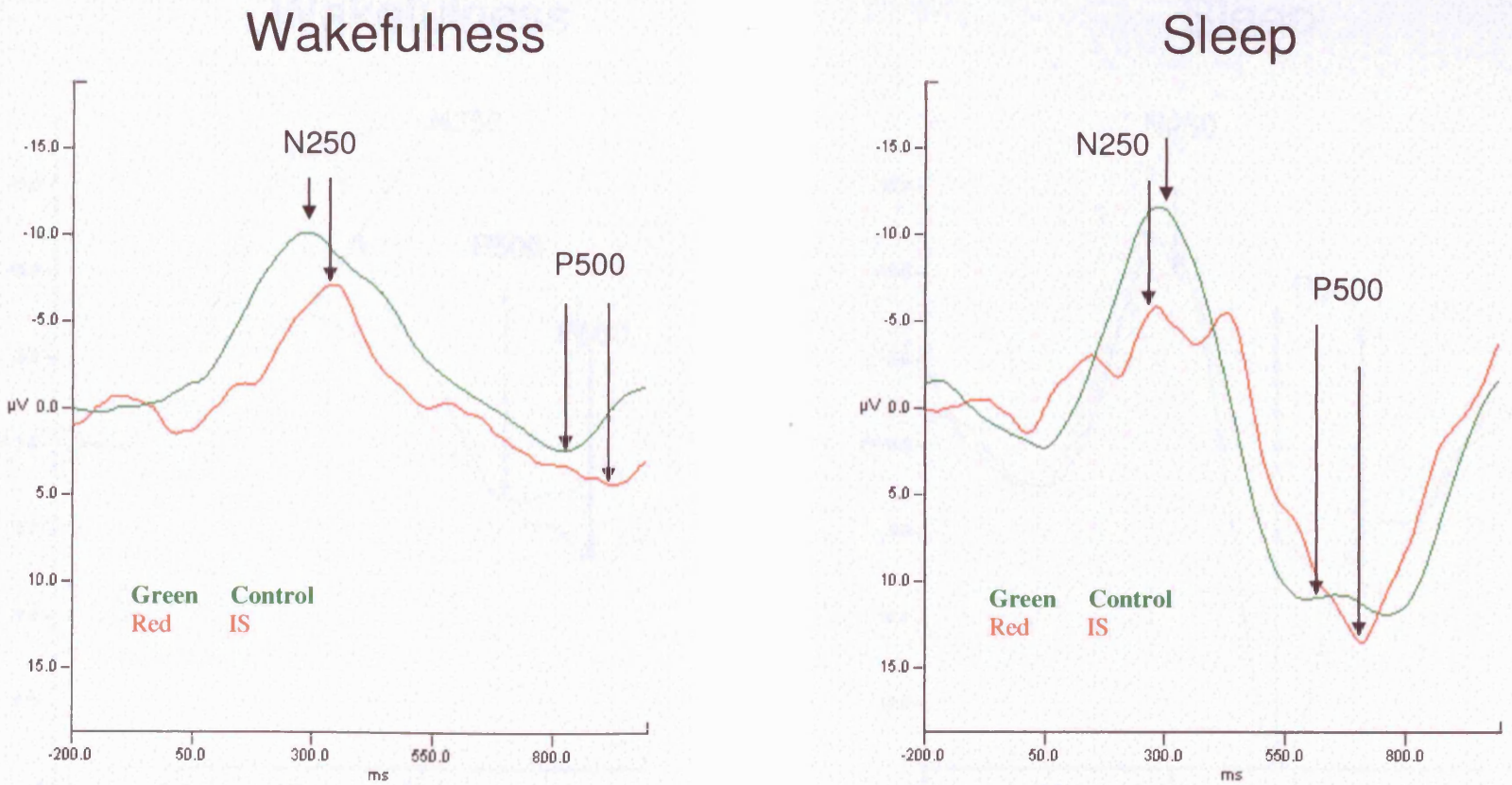


Figure 3.44 shows group mean ERPs of the N250 and P500 in controls (green) compared to IS (red) at 1-4 months during wakefulness and sleep at electrode M1.

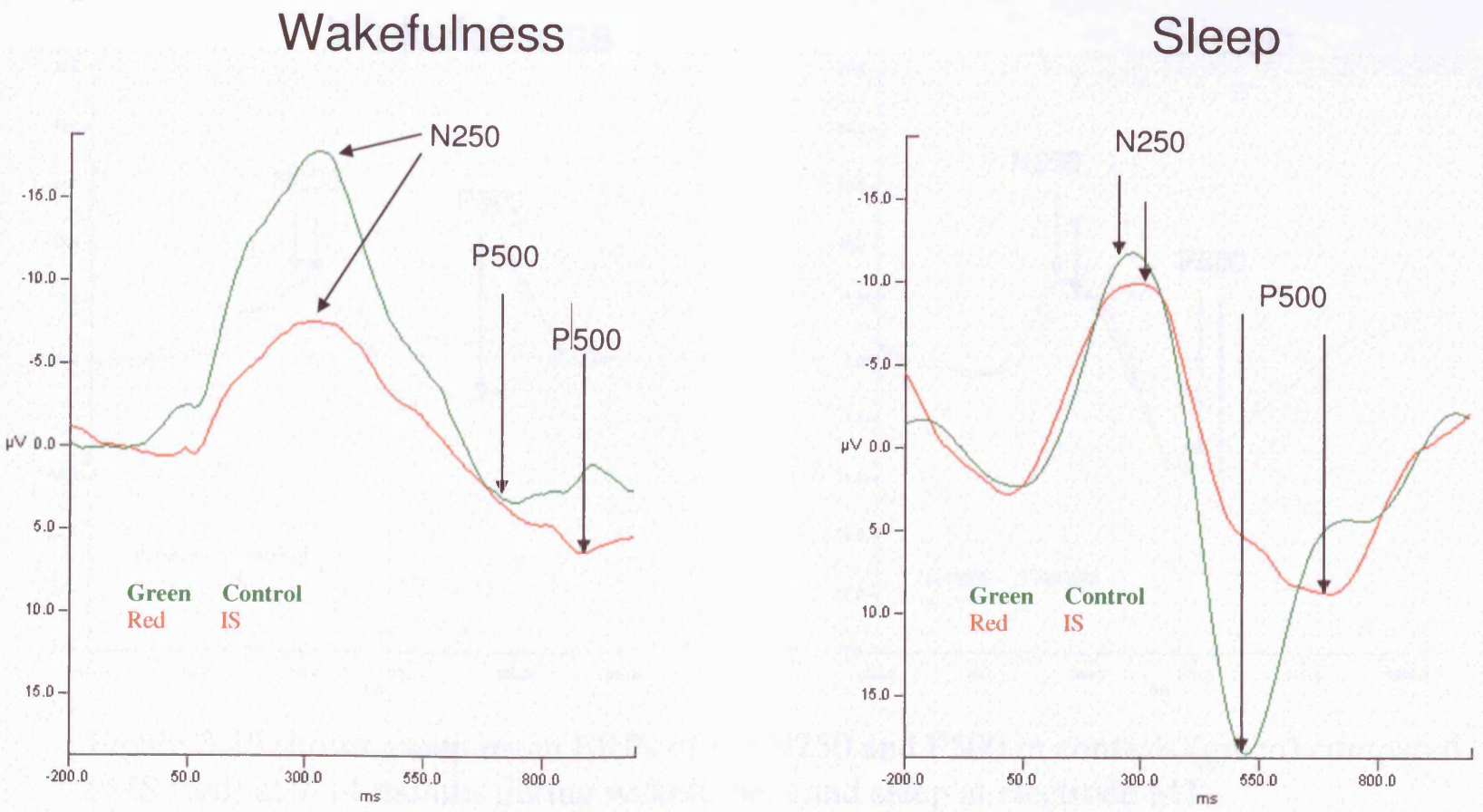


Figure 3.45 shows group mean ERPs of the N250 and P500 of controls (green) compared to IS (red) at 5-8 months during wakefulness and sleep at electrode M1.

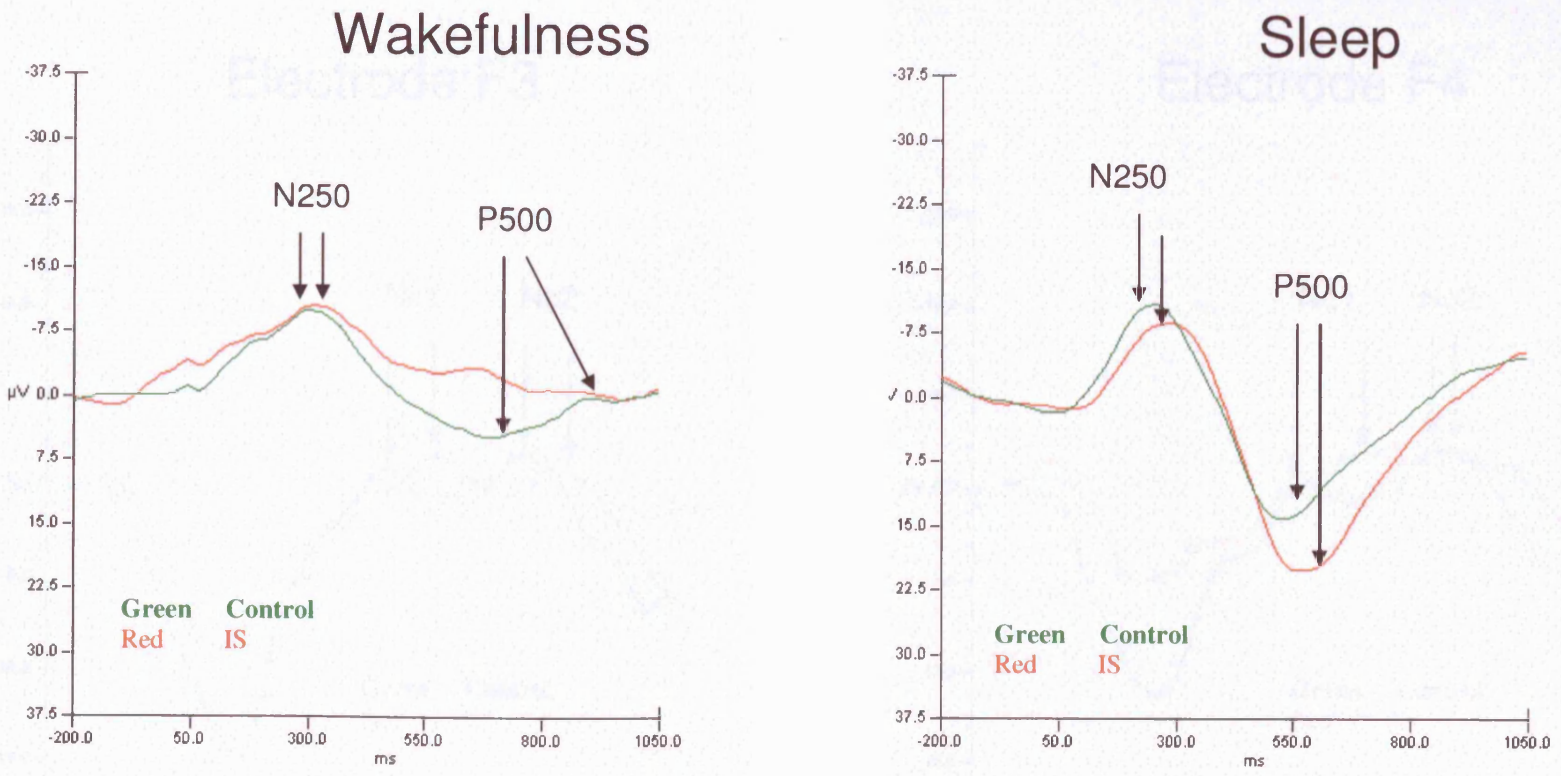


Figure 3.46 shows group mean ERPs of the N250 and P500 in controls (green) compared to IS (red) at 9-14 months during wakefulness and sleep at electrode M1.

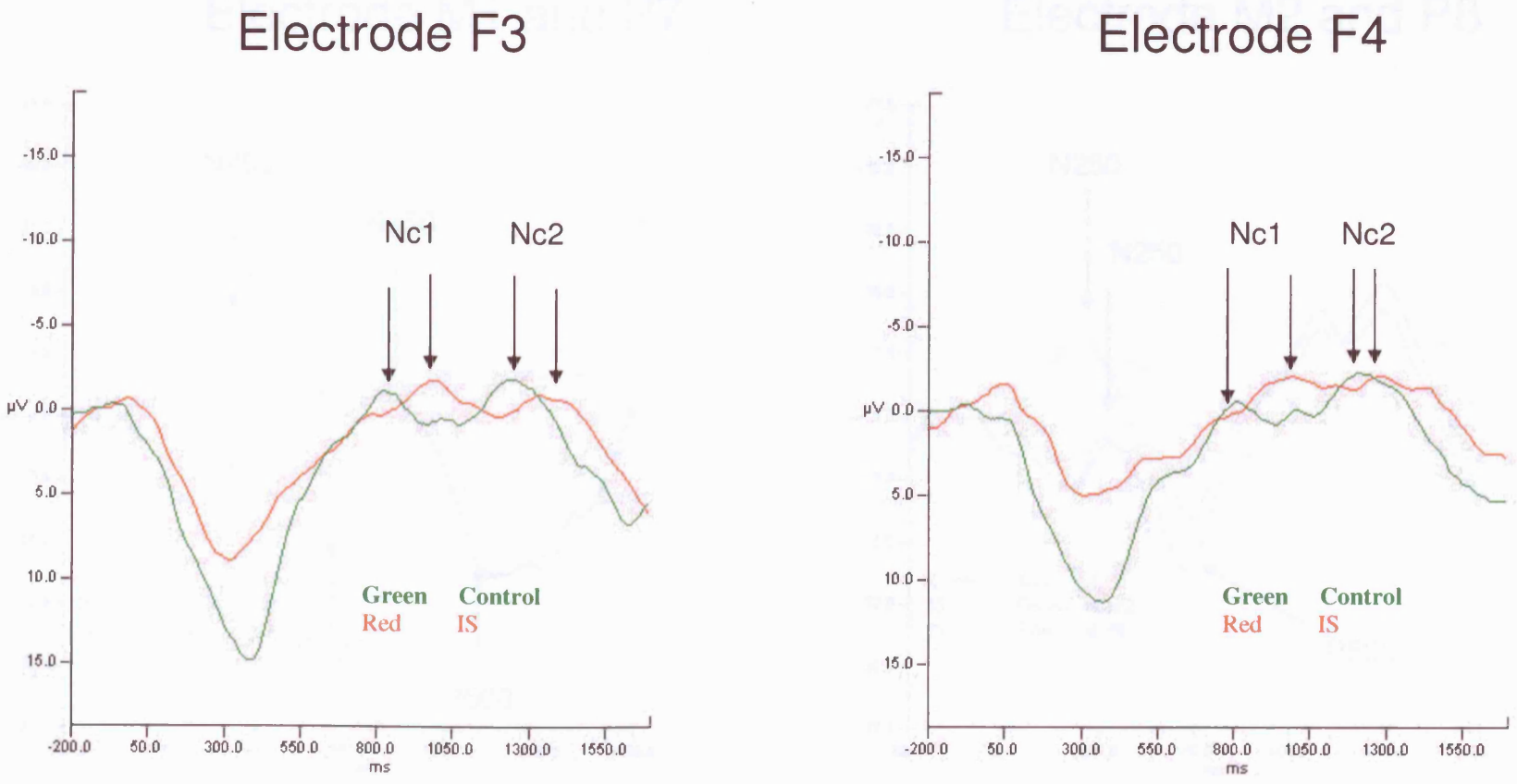


Figure 3.47. shows group mean ERPs of the Nc1and Nc2 in controls (green) compared to IS (red) at 5-8 months in wakefulness at electrode F3 and F4.

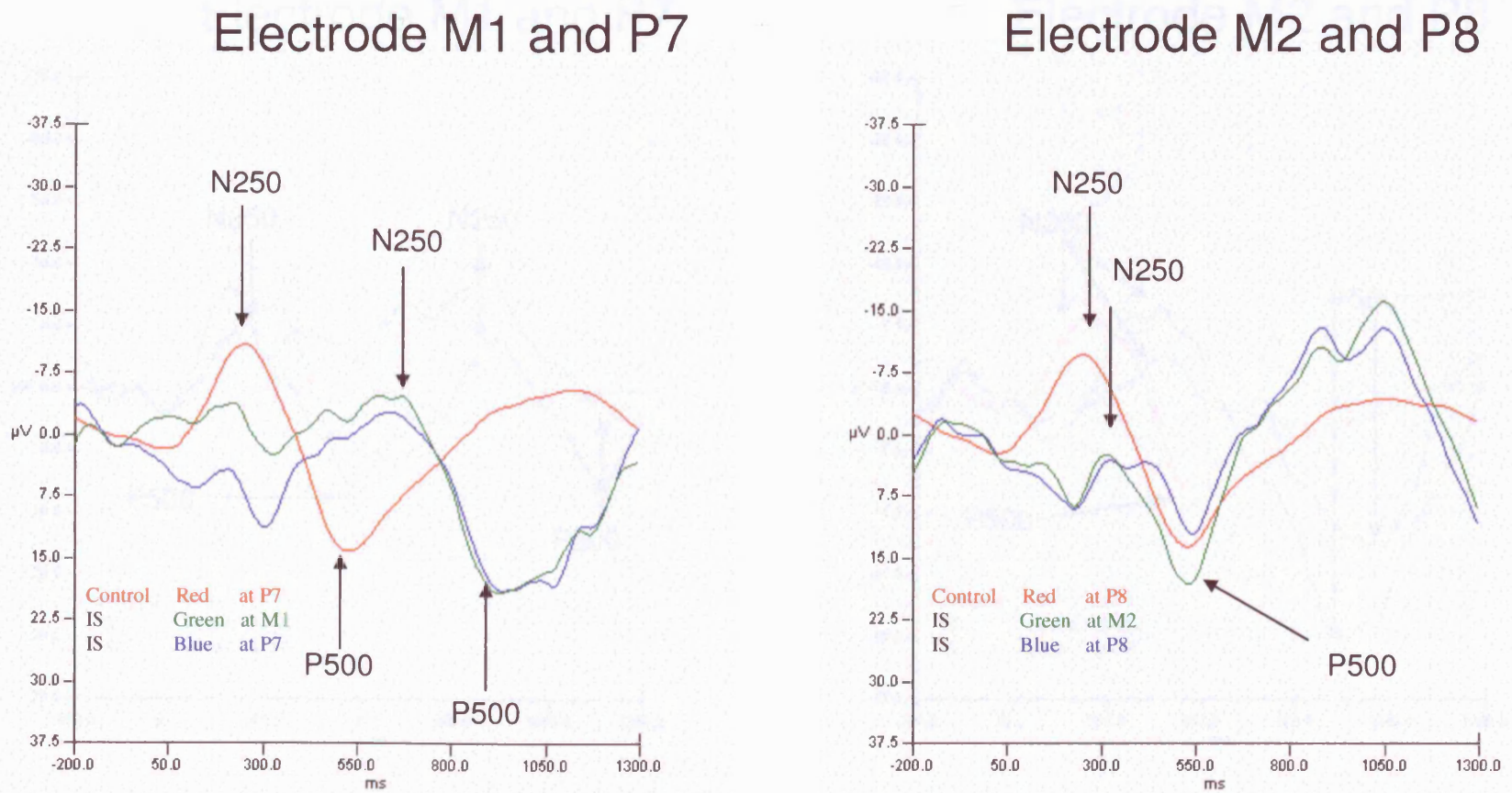


Figure 3.48 shows a patient with IS at 10 months and a R middle cerebral territory infarct with abnormal N250 and P500 components at electrodes M1, M2, P7 and P8 compared to control group (9-14 months) at P7 and P8 in sleep.

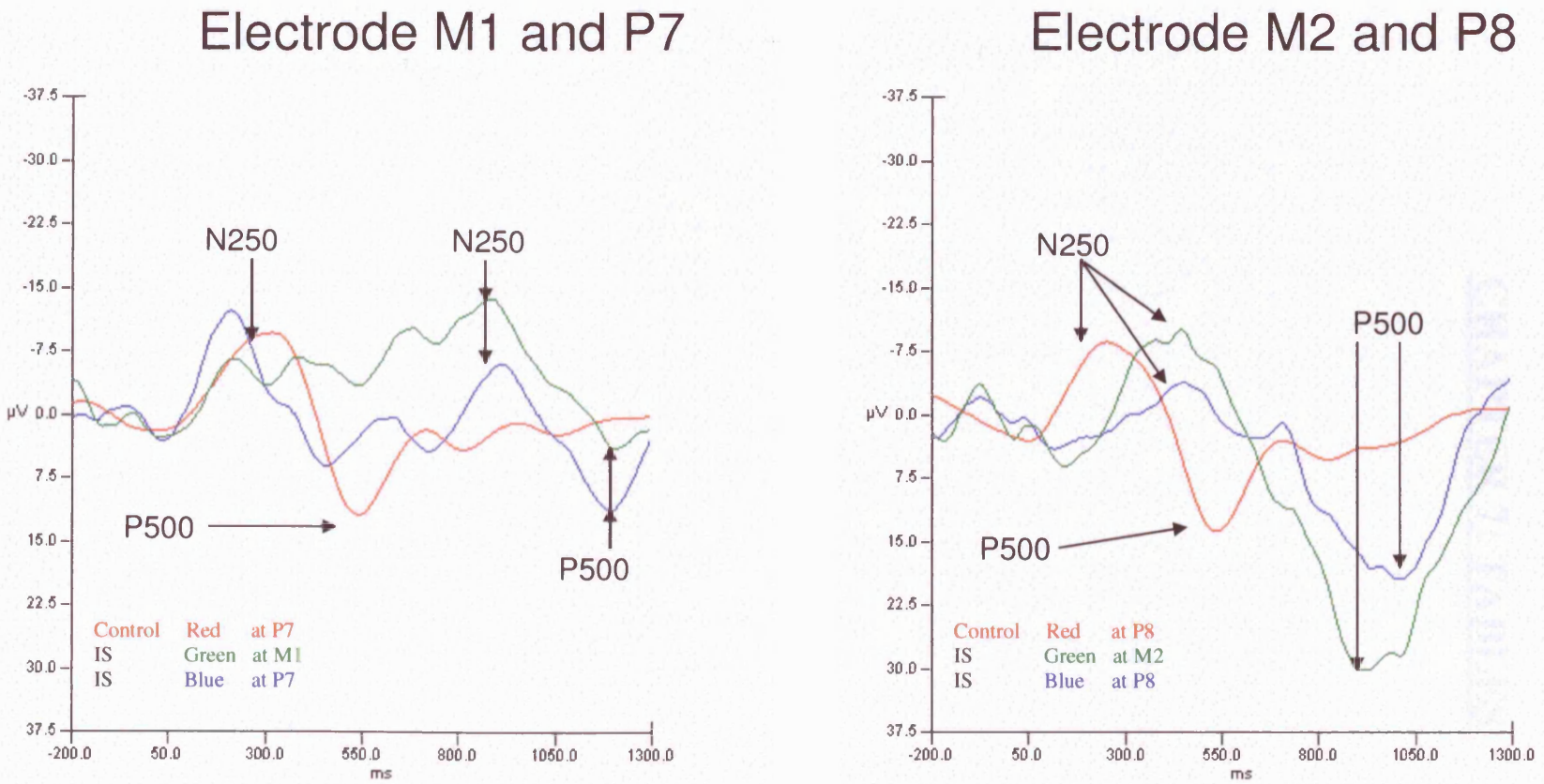


Figure 3.49 shows a patient with IS at 8 months and a R cortical dysplasia and abnormal N250 and P500 components at electrodes M1, P7, M2 and P8 compared to the control group (5-8 months) at P7 and P8 in sleep.

CHAPTER 7: TABLES

Table 1.1. Summary of studies on the infant obligatory auditory ERP components.

Study	Subjects	State	Stimuli	ISI	Recording montage	Developmental findings
(Lenard *et al.*, 1969)	14 full-tem newborns	Not stated	Sine wave Square wave Female human voice	10-15 sec	Bipolar recording T5-Cz, T6-Cz	N2 amplitude larger to square wave sounds and female voice than to sine wave sounds
(Barnet, 1975) Cross-sectional	130 full-term 10 days to 37 months	Asleep Staging	Clicks	2.5 sec	Cz (vertex) referred to joined mastoids	P2-N2 complex stable in infants, with increasing age latency decreases significantly in stage 2 sleep alone and also when *all sleep stages taken together*(P2, N2 and P3), complexity and amplitude increases
(Ohlrich *et al.*, 1978) Longitudinal	16 infants 2 weeks to three years	Asleep Staging	Clicks	2.5 sec	Cz (vertex) referred to joined mastoids	Similar results to the study by Barnet et al 1975 (Cross-sectional)
(Kurtzberg *et al.*, 1984) Longitudinal	35 preterms, 17 at term, 1, 2 and 3 months	Either awake or active sleep	Speech sounds/da/ta/ and simple tones	2.7 sec	Between Fz and Cz ("Cf"); C3 and M1 ("C3M "); C4 and M2 ("C4M"); Oz	Shift from negativity to positivity, with midline preceding lateral and full-terms preceding preterms

(Shucard *et al.*, 1987) Cross-sectional	12 full-term infants at 1, 3 and 6 months	Awake	Sine tones	2-4 sec	T3-Cz, T4-Cz	Complexity and amplitude increase, non-significant latency increase
(Rotteveel *et al.*, 1987) Cross-sectional	65 pre-term at 25-52 weeks at conceptional age	Awake , sleep could not always be avoided	Clicks	2 sec	Active sites Cz, C4', C3' Reference A2, A1 Ground Fz Derivations Cz-A2, Cz-A1, C4'-A2, C3'-A1	Latency of early peaks decreases, adult wave form achieved by 3 months
(Novak *et al.*, 1989) Longitudinal	32 full-terms at term,18 at 1m Mo,14 at 2,15 at 3, and 6 months	Before 1 month either awake or in active sleep, older infants awake	Speech sounds /da/ /ta/ and the corresponding formants	2.7 sec	CF, C3M, C4M, F3, F4, F7, F8, , C3, C4, T5, T6, P3, P4, A1, A2, (Oz)	By 3 months , ERP all sites predominantly positive, P1 and N1 appear and the latency decreases
(Vaughan *et al.*, 1992) Longitudinal	11 full terms: term to 24 months	Not stated	Speech sounds /da/ /ta/	2.7 sec	Between Fz and Cz ("Cf"); C3 and M1 ("C3M "); C4 and M2 ("C4M"); Oz	ERP complexity increases , P2 amplitude maximal at 6 months, followed by a decrease
(Pasman *et al.*, 1999) Cross-sectional	147 infants from 28 weeks to 14 years	Awake , sleep could not always be avoided	Clicks	2 sec	Active sites Cz, C4', C3' Reference A2, A1 Ground Fz Derivations Cz-A2, Cz-A1, C4'-A2, C3'-A1	Disintegration of ERP at 36-41 weeks, from 40 weeks until 4-6 years the P2-N2 complex. A second disintegration at about 6 years, adult like-like P60-N100-P170 by 6-10 years

(Kushnerenko *et al.*, 2002) Longitudinal	15 infants from birth	Awake/ active asleep	Partial harmonic tones	0.7 sec	F3, F4, C3, C4, P3, P4, T3, T4 according to 10-20 system, reference R mastoid	Components identifiable at birth (P150, N250, P350, N450)
(Jing *et al.*, 2006) Longitudinal	5 infants from 3 months to 24 months	awake	2 complex tones with fundamental frequency of 100 or 300 Hz	0.3 sec	62 electrodes, vertex electrode as reference	P150, N250, P350, N450 components decreased with increasing age, N250 and P350 amplitudes reached a maximum at 9 months of age, MMN was not obvious at 3Mo of age, but robust at 6 month of age

ERP component		Age group	Sleep		Awake	
			Left	Right	Left	Right
P150	**Latency** at electrodes F3, F4 (ms)	1-4 months	302 (35)	296 (28)	256 (22)	254 (26)
		5-8 months	252 (27)	253 (28)	218 (20)	207 (22)
		9-15 months	246 (51)	246 (50)	176 (19)	172 (20)
	Side	n.s.			F (1,23)=9.7 , p=0.005	
	Age	F (2,27)= 5.4, p=0.011			F (2,23)=32.7, p<0.001	
	Condition	F (1,22)= 22.9, p<0.001				
	Side	F (1,22)= 5.5, p=0.031				
	Age	F (2,21)= 12.4, p<0.001				
	Amplitude at electrodes F3, F4 (μV)	1-4 months	6.9 (6.3)	6.2 (5.0)	3.9 (2.1)	4.0 (2.1)
		5-8 months	8.8 (5.6)	8.9 (5.5)	5.8 (1.6)	5.3 (2.0)
		9-15 months	7.7 (6.0)	8.0 (5.5)	5.7 (2.1)	6.3 (1.9)
	Side	n.s.			n.s.	
	Age	n.s.			n.s.	
	Condition	F (1,21)= 7.6 p=0.013			.	
	Side	n.s.				
	Age	n.s.				

Table 3.2. Mean (SD) amplitude and peak latency values for the obligatory ERP component P150 across age groups during wakefulness and sleep.

ERP component		Age group	Sleep		Awake	
			Left	Right	Left	Right
N250	**Latency** at electrodes F3, F4 (ms)	1-4 months	373 (28)	379 (17)	373 (52)	367 (54)
		5-8 months	384 (64)	376 (50)	306 (23)	310 (29)
		9-15 months	327 (36)	329 (33)	259 (19)	258 (16)
	Side	n.s			n.s.	
	Age	F (2,20)= 3.8 p=0.041			F (2,20)= 50.0, p<0.001	
	Condition	F (1,15)= 13.6, p<0.004				
	Side	n.s.				
	Age	F (2,14)= 26.5, p<0.001				
	Amplitude at electrodes F3, F4 (μV)	1-4 months	-0.4 (3.1)	-.52 (3.3)	-0.11 (2.5)	-0.11 (2.4)
		5-8 months	1.6 (5.4)	1.7 (4.7)	-0.05 (4.6)	-1.3 (6.2)
		9-15 months	3.7 (3.6)	3.8 (3.7)	0.58 (2.1)	0.43 (2.5)
	Side	n.s.			n.s.	
	Age	n.s.			n.s.	
	Condition	n.s.			.	
	Side	n.s.				
	Age	n.s.				

Table 3.3. Mean (SD) amplitude and peak latency values for the obligatory ERP component N250 across age groups during wakefulness and sleep.

ERP component		Age group	Sleep		Awake	
			Left	Right	Left	Right
P350	**Latency** at electrodes F3, F4 (ms)	1-4 months	504 (35)	493 (43)	443 (27)	445 (35)
		5-8 months	494 (70)	486 (66)	407 (11)	405 (17)
		9-15 months	428 (27)	417 (30)	340 (24)	341 (24)
	Side	F (1,21)= 7.10 p=0.016			n.s.	
	Age	F (2,20)= 6.2 p=0.009			F (2,19)=26.0, p<0.001	
	Condition	F (1,15)= 26.7, p<0.001				
	Side	n.s.				
	Age	F (2,14)=114.9, p<0.001				
	Amplitude at electrodes F3, F4 (μV)	1-4 months	2.8 (1.9)	3.0 (2.0)	2.0 (1.7)	2.0 (1.8)
		5-8 months	5.4 (4.0)	5.0 (3.1)	4.5 (4.6)	4.2 (4.3)
		9-15 months	6.5 (3.9)	6.6 (3.9)	3.7 (3.1)	3.8 (3.2)
	Side	n.s.			n.s.	
	Age	n.s.			n.s.	
	Condition	n.s.			.	
	Side	n.s.				
	Age	n.s.				

Table 3.4. Mean (SD) amplitude and peak latency values for the obligatory ERP component P350 across age groups during wakefulness and sleep.

ERP component		Age group	Sleep		Awake	
			Left	Right	Left	Right
P500	**Latency** at electrodes M1, M2 (ms)	1-4 months	689 (106)	670 (110)	818 (62)	716 (110)
		5-8 months	519 (18)	511 (16)	762 (87)	733 (98)
		9-15 months	517 (44)	520 (44)	666 (88)	539 (105)
	Side	n.s.			F (1,23)=9.9, p=0.005	
	Age	F (2,27)= 17.1 p<0.001			F (2,22)=6.9, p<0.001	
	Condition	F (1,21)= 24.8, p<0.001				
	Side	F (1,21)= 7.5, p=0.014				
	Age	F (2,20)= 12.2, p=0.001				
	Condition x Side	F (1,21)= 7.6, p=0.013				
	Amplitude at electrodes M1, M2 (μV)	1-4 months	13.9 (6.8)	11.8 (5.6)	4.5 (4.6)	6.0 (3.1)
		5-8 months	19.3 (6.9)	14.0 (8.2)	9.2 (3.8)	4.9 (5.7)
		9-15 months	15.4 (8.7)	13.8 (6.9)	5.9 (4.6)	4.4 (4.2)
	Side	F (1,28)= 4.8, p=0.037			F (1,23)=4.9 p=0.038	
	Age	n.s.			n.s; Side x Age: F (1,23)=4.8, p=0.019	
	Condition	F (1,21)= 35.1, p<0.001			.	
	Side	F (1,21)= 7.8, p=0.012				
	Age	n.s.				

Table 3.5. Mean (SD) amplitude and peak latency values for the novelty ERP component P500 across age groups during wakefulness and sleep.

ERP component		Age group	Sleep		Awake	
			Left	Right	Left	Right
Nc1	**Latency** at electrodes F3,F4	1-4 months	722 (99)	687 (97)	842 (37)	839 (33)
		5-8 months	567 (29)	569 (13)	816 (57)	792 (54)
		9-15 months	575 (66)	542 (74)	738 (62)	710 (62)
	Side	F (1,24) = 17 p=0.001			n.s	
	Age	F (2,23) = 8.9 p=0.002			n.s	
	Condition	F (1,19) = 31.0 p<0.001				
	Side	F (1,19) = 7.1 p=0.017				
	Age	F (2,18) = 15.0 p<0.001				
	Amplitude at electrodes F3, F4 (μV)	1-4 months	-7.5 (4.6)	-8.4 (4.8)	-1.9 (1.6)	-2.8 (1.9)
		5-8 months	-10.0 (8.8)	-13 (9.2)	-1.3 (4.9)	-1.6 (2.5)
		9-15 months	-8.8 (5.5)	-12.6 (4.9)	-2.8 (6.0)	-4.9 (4.9)
	Side	F (1,24)=12.6 p=0.002			n.s	
	Age				n.s	
	Condition	F (1,19)=13.3 p=0.002				
	Side	F (1,19)=13.3 p=0.002				

Table 3.6. Mean (SD) amplitude and peak latency values for the novelty ERP component Nc1 across age groups during wakefulness and sleep.

ERP component		Age group	Sleep		Awake	
			Left	Right	Left	Right
Nc2	**Latency** at electrodes F7, F8 (ms)	1-4 months	1059 (177)	1009 (152)	1305 (109)	1305 (139)
		5-8 months	947 (56)	907 (84)	1198 (106)	1217 (121)
		9-15 months	862 (65)	790 (67)	1040 (70)	1002 (82)
	Side				n.s.	
	Age	F (2,23)=8.5 p=0.002			F (2,19)=13.2 p<0.001	
	Condition	F (1,14)= 78 p<0.001				
	Age	F (2,13)= 39 p<0.001				
	Amplitude at electrodes F7, F8 (μV)	1-4 months	-5.2 (8.9)	- 9.8 (6.0)	-2.3 (1.8)	-2.2 (1.5)
		5-8 months	-6.7 (1.5)	- 4.1 (5.2)	-3.8 (1.4)	-4.7 (2.5)
		9-15 months	-4.1 (2.8)	- 5.7 (2.5)	-2.7 (2.4)	-4.3 (2.2)
	Side	n.s.			n.s.	
	Age	n.s.			n.s.	
	Condition	n.s.				

Table 3.7. Mean (SD) amplitude and peak latency values for the novelty ERP component Nc2 across age groups during wakefulness and sleep.

ERP component		Age group	Sleep		Awake	
			Left	Right	Left	Right
P250	**Latency** at electrodes F3, F4 (ms)	1-4 months	352 (71)	372 (38)	279 (62)	272 (51)
		5-8 months	358 (41)	338 (57)	344 (81)	370 (92)
		9-15 months	336 (50)	300 (67)	281 (84)	264 (75)
	Side	n.s.			n.s.	
	Age	n.s.			F (2,23)=4.5, p=0.024	
	Condition	F (1,22)=8.1, p=0.010				
	Side	n.s.				
	Age	n.s.				
	Condition x Age	F (2,21)=4.1 p=0.032				
	Amplitude at electrodes F3, F4 (μV)	1-4 months	12.9 (4.9)	11.1 (3.6)	6.7 (3.3)	5.9 (3.4)
		5-8 months	14.4 (5.6)	13.1 (6.8)	12.6 (4.1)	11.4 (3.0)
		9-15 months	12.3 (7.0)	12.5 (5.8)	9.4 (5.4)	9.1 (4.2)
	Side	n.s.			n.s.	
	Age	n.s.			F (2,23)=5.6, p=0.011	
	Condition	F (1,22)=13.5, p=0.002			.	
	Side	n.s.				
	Age	n.s.				

Table 3.8. Mean (SD) amplitude and peak latency values for the novelty ERP component P250 across age groups during wakefulness and sleep.

ERP component		Age group	Sleep		Awake	
			Left	Right	Left	Right
N250	**Latency** at electrodes M1, M2 (ms)	1-4 months	279 (46)	293 (61)	313 (55)	255 (67)
		5-8 months	285 (40)	263 (41)	315 (57)	325 (52)
		9-15 months	248 (28)	256 (32)	270 (69)	239 (59)
	Side	n.s.			n.s.	
	Age	n.s.			n.s	
	Condition	n.s				
	Side	n.s.				
	Age	n.s.				
	Amplitude at electrodes M1, M2 (μV)	1-4 months	-14.2 (9.6)	-13.5 (6.0)	-9.8 (4.6)	-7.9 (3.2)
		5-8 months	-13.6 (5.1)	-15.9 (6.5)	-16.7 (8.1)	-13.2 (4.1)
		9-15 months	-11.5 (4.7)	-10.7 (4.6)	-10.5 (5.2)	-6.3 (4.8)
	Side	n.s.			F (1,24)=11.1, p=0.003	
	Age	n.s.			F (2,23)= 5.2, p=0.015	
	Condition	n.s.			.	
	Side	n.s.				
	Age	n.s.				

Table 3.9. Mean (SD) amplitude and peak latency values for the novelty ERP component N250 across age groups during wakefulness and sleep.

Table 3.10. Clinical details of patients with infantile spasms.

NR	Patient	Sex	Date of Birth	ERP at age (days) corrected for GA	DBS	R T	Seizure onset of infantile spasms	Seizures before infantile spasms
1	AF	F	15.10.00	318	N	C	6.5 Mo	NO
2	FB	F	21.09.01	319	A	S	4 Mo	NO
3	MK	F	22.11.01	174	A	C	4.6 Mo	NO
4	TM	F	24.05.01	304	A	C	7 Mo	YES
5	EPE	F	22.09.01	279	N	S	6 Mo	NO
6	SP	F	26.09.02	121	A	C	3 Mo	NO
7	FT	F	04.07.00	401	A	C	6 Mo	NO
8	AJ	F	07.09.01	122	A	C	3.6 Mo	NO
9	RK	F	13.02.01	288	A	C	3 Mo	YES
10	SJ	F	05.10.02	214	A	S	4 Mo	NO
11	CB	M	15.02.01	238	A	C	3.6 Mo	YES
12	NH	M	20.07.01	211	A	C	2 Mo	YES
13	HH	M	01.03.02	160	N	S	3.6 Mo	NO
14	KC	M	16.08.02	200	N	C	3 Mo	YES
15	GK	M	20.05.01	172	N	C	3 Mo	NO
16	MK	M	16.05.01	198	N	S	4 Mo	NO
17	BO	M	14.11.01	481	A	C	3 Mo	YES
18	KP	M	10.10.01	50	A	C	1.6 Mo	NO
19	AS	M	26.01.03	191	A	C	2 Mo	YES
20	JSE	M	11.10.00	295	A	C	5 Mo	YES
21	MS	M	25.01.02	109	N	S	3 Mo	YES

22	AV	M	08.11.00	369	A	C	9.6 Mo	NO
23	TW	M	20.09.01	90	A	C	2.6 Mo	YES
24	AO	M	10.08.01	276	A	C	3 Mo	YES
25	GW	M	07.07.01	199	A	C	5 Mo	NO
26	JSH	M	23.10.01	255	A	C	6 Mo	YES
27	JT	M	29.06.03	123	A	C	3.6 Mo	YES
28	JB	M	20.07.01	395	N	C	4 Mo	NO

Table 3.10. F=Female, A=Male, ERP=Event related Potential, DBS =development before onset of spasms, N=Normal, RT=Response to treatment, A=Abnormal, C=continued to have infantile spasms, S=stopped having infantile spasms, GA=gestational age.

Table 3.11. EEG demographics of infants with IS.

NR	Sex	Patient	State	M/S EEG Abnormality	Hyps	EEG more disorganised in sleep	Focal /Multifocal-discharges	Spasms
1	F	AF	A	M	NO		NO	NO
2	F	FB	S	S	YES	YES	MF	NO
	F	FB	A	S	NO		MF	NO
3	F	MKE	S	S	NO	YES	NO	NO
	F	MKE	A	M	NO		NO	NO
4	F	TM	S	S	NO	YES	L FOCAL	NO
	F	TM	A	M	NO		L FOCAL	NO
5	F	EP	S	M	NO	NO	NO	NO
	F	EP	A	M	NO	NO	NO	NO
6	F	SP	S	S	YES	YES	MF	NO
	F	SP	A	S	NO		MF	NO
7	F	FT	S	S	NO	NO	MF	NO
8	F	AJ	S	S	NO	NO	NO	NO
	F	AJ	A	S	NO	NO	NO	NO
9	F	RK	S	S	NO	NO	MF	NO
	F	RK	A	S	NO	N O	MF	YES

10	F	SJ	S	S	NO	NO	R FOCAL	NO
	F	SJ	A	S	NO	NO	R FOCAL	NO
11	M	CB	S	M	NO	NO	NO	NO
	M	CB	A	M	NO	NO	NO	NO
12	M	NH	S	S	YES	NO	R FOCAL	NO
	M	NH	A	S	NO	NO	R FOCAL	NO
13	M	HH	S	M	NO	NO	NO	NO
	M	HH	A	M	NO	NO	NO	NO
14	M	KC	S	S	NO	NO	NO	NO
	M	KC	A	S	NO		NO	NO
15	M	GK	S	S	NO	YES	L FOCAL	NO
	M	GK	A	S	NO		L FOCAL	NO
16	M	MKH	S	M	NO	NO	NO	NO
	M	MKH	A	M	NO	NO	NO	NO
17	M	BO	S	M	NO		L FOCAL	NO
18	M	KP	A	S	NO		L FOCAL	NO
19	M	AS	S	M	NO	NO	NO	NO
	M	AS	A	M	NO	NO	NO	NO
20	M	JSE	S	M	NO	NO	NO	NO
	M	JSE	A	M	NO	NO	N O	NO

21	M	MS	S	M	NO	NO	L FOCAL	NO
	M	MS	A	M	NO	NO	L FOCAL	NO
22	M	AV	S	M	NO	NO	NO	NO
	M	AV	A	M	NO	NO	NO	NO
23	M	TW	S	S	NO	YES	L FOCAL	NO
	M	TW	A	S	NO		L FOCAL	NO
24	M	AO	S	S	NO	YES	MF	NO
	M	AO	A	S	YES	NO	MF	NO
25	M	GW	S	S	NO	NO	L FOCAL	NO
	M	GW	A	S	NO	NO	L FOCAL	NO
26	M	JSH	S	S	NO	NO	MF	NO
	M	JSH	A	S	NO	NO	MF	YES
27	M	JT	S	S	NO	N O	MF	NO
	M	JT	A	S	NO	N O	MF	NO
28	M	JB	S	S	YES	YES	MF	NO

Table 3.11. A (awake), S (stage II sleep), F=female, M=male
L FOCAL (L focal discharges), R FOCAL (R focal discharges), MF (multifocal discharges), M (Moderate EEG abnormality), S (Severe EEG abnormality), Hyps (Hypsarrythmia).

Table 3.12. MRI aetiology.

Infants with infantile spasms			Aetiology of infantile spasms				
NR	Name	Sex	**Cryptogenic**	**Symptomatic**			
			Normal	Cortical Dysplasia	Tuberous Sclerosis (TS)	Hypoxic Ischaemic (HI)	Others
1	AF	F	Normal				
2	FB	F					Microcephaly Delayed Myelination
3	MK	F					Trisomie 21
4	TM	F			TS		
5	EP	F	Normal				
6	SP	F		Aicardi –Syndrome			
7	FT	F				R middle cerebral territory infarct/ L hemisphere intact	
8	AJ	F		Lissencephaly Miller-Dieker Syndrome			
9	RK	F		Proteus Syndrome/L hemimegalencephaly Gross megencehaly (also R side of the brain)			

10	SJ	F				IVH grade II bilaterally Periventricular Leukomalacia	
11	CB	M		L sylvian fissure abnormality			
12	NH	M		Cortical dysplasia/ of the R inferior parietal lobule extending into the angular gyrus region			
13	HH	M	Normal				
14	KC	M	Normal				
15	GK	M	Normal				
16	MK	M	Normal				
17	BO	M			TS		
18	KP	M		L parietal cortical dysplasia			
19	AS	M				HI	
20	JS	M					Delayed Myelination
21	MS	M			TS		

22	AV	M	Normal				
23	TW	M		L occipital and posterior parietal region, L temporal occipital			
24	AO	M				HI	
25	GW	M					Delayed Myelination Absent corpus callosum
26	JSH	M				HI	
27	JT	M				HI	
28	JB	M	Normal				

Table 3.12. F=female, M=male.

Table 3.13. Amplitude of background activity of the EEG in patients with IS and averages used in the analysis.

Nr	Patient	Background activity (μV)		Obligatory averages		Novel averages		Aetiology
		Sleep	Awake	Sleep	Awake	Sleep	Awake	
1	FA		50		1249		139	N
2	FB	75	50	1262	1664	146	204	other
3	CB	75	50	552	1223	128	139	CD
4	JB	200	75	2154	NS	255	NS	N
5	NH	100	100	1292	NS	154	NS	CD
6	HH	100	25	1317	1046	153	123	N
7	KC	75	75	NS	1295	134	159	N
8	MK	75	50	607	1244	72	147	other
9	GK	75	50	NS	1076	71	176	N
10	MKH	75	50	1381	NS	161	NS	N
11	TM	100	50	NS	1196	71	145	TS
12	BO	150		NS		228		TS
13	KP		50		1144		215	CD
14	EP	50	25	1949	1068	231	129	N
15	SP	150	150	NS	NS	163	405	CD
16	AS	50	25	1257	1043	149	202	HI
17	JSH	150	50	638	1976	76	230	HI
18	MS	50	50	1328	2020	161	229	TS

19	FT	150		1660		198		HI
20	AV	75	25	686	1068	165	NS	N
21	TW	150	200	NS	1214	71	144	CD
22	AO	100	100	NS	NS	NS	NS	HI
23	AJ	250	250	NS	NS	NS	NS	CD
24	GW	100	75	NS	NS	NS	NS	other
25	JS	75	50	NS	NS	NS	NS	other
26	RK	300	300	NS	NS	NS	NS	CD
27	JT	75	75	NS	NS	NS	NS	HI
28	SJ	75	150	NS	NS	NS	NS	HI

Table 3.13. NS= No signal, XX=The novelty signal was abnormal despite normal background activity, CD=cortical dysplasia, HI=hypoxic ischaemic, TS=tuberous sclerosis, N =normal brain scan, Other= see table 12 MRI Aetiology for detailed information.

Amplitude of background activity	±25μV	±50μV	±75μV	±100μV	±200μV	±300μV
Novel ERP P-to-P-AM Awake	30μV	30μV	30μV	30μV	30μV	30μV
S/N Ratio	2.4	2.1	2.0	2.1	2	2
Number of stimulus repetitions (blocks) required	16	49	100	196	729	1600
Obligatory ERP P-to-P-AM	7μV	7μV	7μV	7μV	7μV	7μV
S/N Ratio	2	2	2	2	2	2
Number of stimulus repetitions (blocks) required	225	841	1849	3364	13225	29584

Table 3.14. Signal to Noise Ratio in awake infants with infantile spasms, S/N Ratio (signal to noise ratio), P-to-P-AM (peak to peak amplitude).

Amplitude of background activity	±50μV	±75μV	±100μV	±150μV	±250μV	±300μV
Novel ERP P-to-P-AM asleep	50μV	50μV	50μV	50μV	50μV	50μV
S/N Ratio	2	2	2	2	2	2
Averages (blocks) required	16	36	64	162	400	576
Obligatory ERP P-to-P-AM	10μV	10μV	10μV	10μV	10μV	10μV
S/N Ratio	2	2	2	2	2	2
Number of stimulus repetitions (blocks) required	400	900	1600	3600	10000	14400

Table 3.15. Signal to Noise Ratio in sleeping infants with infantile spasms, S/R (signal to noise ratio), P-to-P-AM (peak to peak amplitude).

Component	Controls (n=30)	Infantile Spasms (n=26)	χ^2	P
P150 S	30/30 100%	13/26 50%	19.5	<0.001
P150 A	26/26 100%	13/26 50%	17.3	<0.001
N250 S	23/30 76%	5/26 19%	18.3	<0.001
N250 A	23/26 88%	9/26 34%	18.6	<0.001
P350 S	23/30 76%	6/26 23%	16.0	<0.001
P350 A	22/26 84%	9/26 34%	13.4	<0.001
Novel S	29/30 96%	16/26 61%	10.8	<0.001
Novel A	23/26 88%	11/26 42%	17.3	<0.001

Table 3.16. Presence of obligatory components P150, N250 and P350 and novelty components in control infants during wakefulness (A) and sleep (S) compared to infants with IS.

AEP	Moderate EEG abnormality	Severe EEG abnormality	P
Obligatory present			
Sleep (13/26)	8 (30%)	5 (19%)	0.004
Wakefulness (14/26)	10	4 (15%)	0.005
Obligatory absent			
Sleep (13/26)	1 (3,8%)	12 (46%)	
Wakefulness (12/26)	1 (3,8%)	11 (42%)	
Novel present			
Sleep (19/26)	9 (34%)	10 (38%)	0.03
Wakefulness (15/26)	9 (34%)	6 (23%)	0.02
Novel absent			
Sleep (7/26)		7 (26%)	
Wakefulness (11/26)	2 (7%)	9 (34%)	

Table 3.17. Presence or absence of obligatory and novel auditory ERPs during wakefulness and sleep in a moderate or severe abnormal EEG.

ERP component		Infantile spasms Mean +/- (SD)		Controls Mean +/- (SD)		Spearman		p-value	
		Sleep	Awake	Sleep	Awake	Sleep	Awake	Sleep	Awake
N250 Latency	msec	321 (95)	363 (118)	267 (33)	284 (47)	0.404	0.457	**0.008**	**<0.001**
N250 Amplitude	μV	-21.4 (16.6)	-16.8 (6.5)	-22.0 (7.3)	-18.1 (8.5)	0.177	0.064	0.689	0.299
P150 Latency	msec	394 (87)	298 (95)	262 (44)	207 (38)	0.666	0.488	**<0.001**	**<0.001**
P150 Amplitude	μV	11.0 (7.7)	4.4 (13)	7.8 (5.4)	4.7 (2.0)	-.215	0.192	0.183	0.218
P500 Latency	msec	692 (152)	950 (193)	585 (91)	729 (74)	0.666	0.488	**<0.001**	**<0.001**
P500 Amplitude	μV	19.6 (18.7)	7.7 (3.6)	14.2 (5.6)	6.5 (4.1)	0.141	0.140	0.378	0.343
NcS Latency	msec	667 (164)		546 (81)		0.034		**<0.001**	
NcS Amplitude	μV	-15.9 (13.6)		-14.4 (6.1)		0.556		0.818	
Nc1 Latency	msec	In data	698 (180)	In data	558 (86)	In data	0.672	In data	**<0.0001**
Nc1 Amplitude	μV	In data	-.53 (2.9)	In data	-.13 (2.6)	In data	-.150	In data	0.363
Nc2 Latency	msec	1182 (220)	1156 (201)	732 (143)	1164 (150)	0.113	0.519	0.539	**0.001**
Nc2 Amplitude	μV	-8.5 (5.8)	-8.3 (5.9)	-5.5 (3.7)	-2.9 (2.4)	0.451	0.206	0.01	0.220
P2a Latency	msec	In data	In data	In data	In data	In data	In data	In data	In data
P2a Amplitude	μV	9.7 (8.0)	7.17 (3.5)	12.7 (5.0)	9.3 (4.4)	-.252	-.295	0.107	0.042
P2b Latency	msec	494 (129)	540 (252)	409 (98)	386 (91)	0.331	In data	0.040	In data
P2b Amplitude	μV	14.0 (12.5)	7.0 (4.0)	10.6 (5.0)	8.8 (4.9)	In data	0.100	In data	0.519
N250 Latency	msec	474 (178)	410 (147)	354 (49)	302 (55)	0.464	0.306	0.006	0.113
N250 Amplitude	μV	4.7 (3.5)	1.4 (3.5)	2.1 (3.9)	3.2 (2.9)	In data	0.352	In data	0.066
P350 Latency	msec	616 (219)	513 (160)	462 (60)	386 (52)	0.418	0.421	0.017	0.018
P350 Amplitude	μV	5.9 (4.0)	3.2 (2.7)	5.3 (3.1)	3.2 (2.9)	0.094	0.153	0.608	0.429

Table 3.18. Latencies and amplitudes in infants with IS compared to control infants, P-values remaining significant post correction are in bold, in data=insufficient data.

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APPENDICES

Parent Information (normal controls)

DEVELOPMENT OF LANGUAGE POTENTIALS

We would like to ask your permission to include your child in this project.

The aim of the study

The aim of the study is to see whether infantile spasms, a type of epilepsy that begins in first year of life, can slow the children's learning and speech. We are suggesting that this form of epilepsy interferes with the language centres in the brain. This may lead to new forms of treatment for infantile spasms.

Why is the study being done?

Babies with infantile spasms often develop difficulties with learning, speech and general development. This study will try to understand the way that the epilepsy causes such problems.

How is the study to be done?

Your baby will be admitted to the Neurology unit at Great Ormond Street Hospital to have an EEG (electroencephalogram). Electrodes will be attached to the head to record brain activity. Your baby will be seated in a safety seat and electrodes will be attached to the head using an elastic cap. Sounds like ta and da will be played to both ears of your child via speakers at a distance of 30 cm. The sound will include a bird, cat or a dog. The tests will take approximately 1 hour.

What are the risks and discomfort?

No risks to your child can be foreseen. There is no discomfort wearing the elastic cap with the electrodes on the head.

Who will have access to the case/records?

Only the researchers and a representative of the Research Ethics Committee will have access to the data collected during this study.

The use of some types of personal information is safeguarded by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. If you have any questions about data protection, contact the Data Protection Officer via the switchboard on 020 7405 9200 extension 5217.

What are the arrangements for compensation?

This research has been approved by an independent Research Ethics Committee who believe that it is of minimal risk to the child. However, research can carry unforeseen

risks and you are informed of your rights in the unlikely event that any harm should occur as a result of taking part in this study.

No special compensation arrangements have been made for this project but you have the right to claim damages in a court of law. This will require you to prove a fault on the part of the Hospital and/or any manufacturer involved.

What are the potential benefits?

This study will not bring any immediate benefits to your child. However if we can show that the temporal lobe of the brain is affected in children with infantile spasms, it may be possible in the future to protect the temporal lobe in children with infantile spasms and prevent developmental delay.

Do I have to take part in this study?

If you decide, now or at a later stage, that you do not wish to participate in this research project, that is entirely your right and will not in any way prejudice any present or future treatment.

Who do parents speak to if problems arise?

If you have any complaints about the way in which this research project has been, or is being conducted, please, in the first instance, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via the Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, or if urgent, by telephone on 020 7905 2620 and the Committee administration will put you in contact with him.

Researcher who will have contact with the family

Dr Klaus Werner, Honorary Research Fellow, Neurosciences Unit, The Wolfson Centre.Professor Brian Neville, Professor of Paediatric Neurology, GOSH

Details of how to contact the researcher

The Wolfson Centre, Mecklenburgh Square, London WC1N 2AP
Tel: 020 7837 7618

REC No. 01NR05

Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee

Consent Form for PARENTS OR GUARDIANS of Children Participating in Research Studies

Title: Mechanisms for cognitive impairment in the syndrome of infantile spasms and other early-onset epilepsies.

NOTES FOR PARENTS OR GUARDIANS

1. Your child has been asked to take part in a research study. The person organising that study is responsible for explaining the project to you before you give consent.

2. Please ask the researcher any questions you may have about this project, before you decide whether you wish to participate.

3. If you decide, now or at any other stage, that you do not wish your child to participate in the research project, that is entirely your right, and if your child is a patient it will not in any way prejudice any present or future treatment.

4. You will be given an information sheet which describes the research project. This information sheet is for you to keep and refer to. ***Please read it carefully.***

5. If you have any complaints about the way in which this research project has been or is being conducted, please, in the first instance, discuss them with your researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via The Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH or if urgent, by telephone on 020 7905 2620 and the committee administration will put you in contact with him.

CONSENT

I/We _____, being the parent(s)/guardian)s) of

_____ agree that the Research Project named above has been explained to me to my/our satisfaction, and I/We give permission for our child to take part in this study. I/We have read both the notes written above and the Information Sheet provided, and understand what the research study involves.

SIGNED (Parent(s)/Guardian(s)) **DATE**

....

SIGNED (Researcher) **DATE**

....

REC No. 01NR05

NOTES FOR THE RESEARCHER

It is your responsibility to ensure that the parents/guardians and child (it mature enough) understand what the research project involves, both theoretically and practically. **You must allow sufficient time to do this.** You must make the judgement of whether or not the child can understand the project. Age alone is not important. Make sure that the relatives or child can contact you if they have additional questions.

A copy of this completed form must be placed in the patient's clinical records and a copy must be kept by you with the research records.

If there are any unforeseen ethical problems with this study you must inform the Chairman of the Research Ethics Committee immediately (via The Research and Development Office, ICH on 0171 905 2620) and follow this up in writing.

Parent Information (infantile spasms)

THE EFFECT OF INFANTILE SPASMS ON THE DEVELOPMENT OF LANGUAGE

We would like to ask your permission to include your child in this project.

The aim of the study

The aim of the study is to see whether infantile spasms, a type of epilepsy that begins in first year of life, can slow the children's learning and speech. We are suggesting that this form of epilepsy interferes with the language centres in the brain. This may lead to new forms of treatment for infantile spasms.

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Researcher who will have contact with the family

Dr Klaus Werner, Honorary Research Fellow, Neurosciences Unit, The Wolfson Centre.
Professor Brian Neville, Professor of Paediatric Neurology, GOSH

Details of how to contact the researcher

The Wolfson Centre, Mecklenburgh Square, London WC1N 2AP
Tel: 020 7837 7618

REC No. 01NR05

Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee

Consent Form for PARENTS OR GUARDIANS of Children Participating in Research Studies

Title: Mechanisms for cognitive impairment in the syndrome of infantile spasms and other early-onset epilepsies.

NOTES FOR PARENTS OR GUARDIANS

6. Your child has been asked to take part in a research study. The person organising that study is responsible for explaining the project to you before you give consent.

7. Please ask the researcher any questions you may have about this project, before you decide whether you wish to participate.

8. If you decide, now or at any other stage, that you do not wish your child to participate in the research project, that is entirely your right, and if your child is a patient it will not in any way prejudice any present or future treatment.

9. You will be given an information sheet which describes the research project. This information sheet is for you to keep and refer to. ***Please read it carefully.***

10. If you have any complaints about the way in which this research project has been or is being conducted, please, in the first instance, discuss them with your researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via The Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH or if urgent, by telephone on 020 7905 2620 and the committee administration will put you in contact with him.

CONSENT

I/We _____, being the parent(s)/guardian)s) of

_____ agree that the Research Project named above has been explained to me to my/our satisfaction, and I/We give permission for our child to take part in this study. I/We have read both the notes written above and the Information Sheet provided, and understand what the research study involves.

SIGNED (Parent(s)/Guardian(s)) **DATE**

....

SIGNED (Researcher) **DATE**

....

REC No. 01NR05

NOTES FOR THE RESEARCHER

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If there are any unforeseen ethical problems with this study you must inform the Chairman of the Research Ethics Committee immediately (via The Research and Development Office, ICH on 0171 905 2620) and follow this up in writing.

Name DB
Age at investigation (ERP) in days
Time from first seizure to ERPs
Age onset of first seizure
First seizure description
Age onset of IS
Subsequent seizures after ERP description Response to treatment
Seizure frequency prior to administration of AEDs per week
Which AED before ERP When ERP Which AED afterwards
Developmental Delay prior to IS
Developmental Delay during IS/ cognitive regression
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Visual alertness
Metabolic investigations Infectious scren
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The identical sequence was used in all recordings
A=standard, B=pre-deviant, C=deviant, N=novel stimulus